Observational and Experimental Studies on the Diagnosis and Outcome of Epilepsy and Epileptogenic Conditions: Investigating the Static and Dynamic Phenotype of Epilepsy

Thesis

Observational and experimental studies on the diagnosis and outcome of epilepsy and epileptogenic conditions.

Investigating the static and dynamic phenotype of epilepsy.

Thesis submitted for the degree of

Doctor of Philosophy

Disciplines of Life and Biomolecular Sciences

Open University of Milton Keynes, United Kingdom

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September, 2017

Preface

The main body of this study was perfomed at the IRCCS-Institute for Pharmacological Research "Mario Negri", Milan, Italy, during the years 2014-2017, under the direction of Dr. Ettore Beghi and the external supervision of Prof. Josemir W. Sander (*Professor* of Neurology and Clinical Epilepsy, Univeristy College London, UK) and Dr. Ugo Lucca (Laboratory of Geriatric Neuropsychiatry, Department of Neuroscience, IRCCS-Institute for Pharmacological Research "Mario Negri").

Declaration

This thesis has not been submitted in whole or in part for a degree or diploma or other qualification at any other University.

The experimental work described and the original data obtained were performed by myself and includes work done in collaboration with: Prof. Giuseppe Erba from the University of Rochester that enrolled patients for the MI-RO Study; Dr. Paolo Bonanni, Dr.ssa Giovanna Randazzo from IRCCS E. Medea of Conegliano Veneto and Dr. Maurizio Elia from IRCCS Oasi Maria SS, Troina that enrolled patients in the validation study of idic(15) syndrome; Dr. Peter Bergin, from the University of Auckland, New Zealand, who designed the EPINET Study; Dr Elisa Bianchi who provided statistical analysis for all the presented projects.

Abstract

Different studies spanning the diagnosis, the outcome and the treatment of the disease have been performed to investigate the spectrum of epilepsy. The topics were: 1. The differential diagnosis between epilepsy and another common clinical condition (PNES); 2. The verification if epilepsy could be a marker of genetic diseases characterized by intellectual disability and behavioural abnormalities (idic(15) syndrome); 3.The assessment of the long-term outcome of the disease to identify different prognostic patterns; 4.The investigation of the frequency and clinical features of drug-resistant epilepsy (DRE) with reference to the number of antiepileptic drugs (AEDs).

In 1/3 of cases a confident diagnosis of PNES/ES can be established by epileptologists on video data only. Compared to epileptologists, psychiatrists demonstrated to be less accurate in diagnosing PNES but more attuned to capture the subtleties of human behaviour. Investigating the patients and their witnesses using ad-hoc structured questionnaires, some variables were highly predictive of PNES diagnosis. These instruments may be useful clinical tools in settings not offering the facilities for a correct diagnosis and in cases where video-EEG monitoring has failed. In the study on the characterisation of idic(15) syndrome, epilepsy was used as disease tracer. It was found to be one of the few symptoms with satisfactory agreement but not a marker of this genetic syndrome. To verify if the epilepsy course and treatment response is static or dynamic, a population based-study in a well-defined area of Italy was performed. DRE patients (1/6 patients with active epilepsy in the general population) can reach 2-year remission (24.9 %) at 20 years and also early terminal remission (1.3%). AEDs given at diagnosis are retained in the majority of cases and the withdrawal can be predicted by age at diagnosis, sex, disease characteristics and varies among drugs.

Acknowledgments

I would like to thank my Director of Studies and Head of Laboratory, Dr. Ettore Beghi for his guidance before and during the PhD program, and my supervisors, Prof. Josemir W. Sander, who helped me with in the discussion of study data and publications, and Ugo Lucca for his critical appraisal of my work. I would also thank the examiners, Dr. Maurizio Bonati, Dr. Gianluigi Forloni and Prof. Markus Reuber for their suggestions during the thesis discussion.

A special thank goes to Dr Elisa Bianchi who provided statistical analysis for all the presented projects and answered many times to my questions about statistics; Prof. Giuseppe Erba from the University of Rochester that enrolled patients for the MI-RO Study who enriched my epileptological background with hist experience and enless enthusiasm; Dr. Paolo Bonanni, Dr.ssa Giovanna Randazzo from IRCCS E. Medea, Conegliano Veneto, and Dr. Maurizio Elia from IRCCS Oasi Maria SS, Troina, that encouraged patients and their families to participate in the study of characterization of idic(15) syndrome; Dr. Peter Bergin, from the University of Auckland, New Zealand, who designed the EPINET Study and let me to be involved in his fascinating project.

Many thanks to my collegues Dr. Elisabetta Pupillo and Mrs. Susanna Franceschi for having borne me during these years.

Last but not least, I would also like to thank Andrea, my husband, for his support and Alessio, my son, for having “torn” my life, my parents Paola and Alberto and my sisters Chiara and Greta for having always supported me during the entire PhD scholarship.

List of abbreviations

AED = Antiepileptic drug

ALS = Amyotrophic lateral sclerosis

AS = Angelman syndrome

BP = Breakpoint (region)

BSC= Barbexaclone

CBZ = Carbamazepine

CI = Confidence Interval

CLB = Clobazam

CNP =Clonazepam

CRF = Case record form

CT = Computerized Tomography

DRE= Drug-Resistant Epilepsy

EEG = Electroencephalogram

EKG = Electrocardiography

ES = Epileptic seizures

ESM = Ethosuximide

FDA= Food and drug administration

FISH = Fluorescence in situ hybridization

GBP = Gabapentin

GCP = Good clinical practice

GP = General Practitioner

GPL3 = General public licence 3

GS = Gold Standard

HR = Hazard Ratio

ICH = International conference on harmonization

Idic(15) = 15q11-13 duplication syndrome

IEC = Independent ethics committee

ILAE = International League Against Epilepsy

IRB = Institutional review board

IRCCS = Istituto di Ricerca e Cura a Carattere Scientifico

LCR = Low copy repeat

LEV = Levetiracetam

LTG = Lamotrigine

MD = Medical Doctor

MI-RO = Milano – Rochester

MRI = Magnetic Resonance Imaging

NAHR = Non allelic homologous recombination

NDD = No definite diagnosis

NES = Non-epileptic seizures

NGPSE = National General Practice Study of Epilepsy

OXC = Oxcarbazepine

OR = Odds ratio

PB = Phenobarbital

PHT= Phenytoin

PGB = Pregabalin

PNES = Psychogenic-non epileptic seizures

PRM = Primidone

PS = Psychiatrist

PWS = Prader-Willi syndrome

R = Rater

REB = Research ethics board

SD = Standard Deviation

SE = Sensitivity

SP = Specifity

SMC = Supernumerary marker chromosome

SMR = Standardized mortality ratio

TGB = Tiagabine

TPM =Topiramate

VEM = Video-EEG monitoring

VGB =Vigabatrin

VPA = Valproate

VPM = Valpromide

UK = United Kingdom

URI = Upper respiratory infections

USA= United States of America

ZNS = Zonisamide

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1. Background and rationale

1.1 The disease

Epilepsy is a symptom complex arising from an altered brain function, which may be secondary to a variety of structural or functional changes to the central nervous system (CNS). The cardinal manifestations of epilepsy are the epileptic seizures, recurrent paroxysmal events characterized by stereotyped behavioural alterations reflecting the neural mechanisms involved by the epileptic process. In most cases, the disease can be diagnosed through a careful history or by the observation of a seizure. The interictal electroencephalogram (EEG) is of limited value in making the diagnosis, as highlighted in a meta-analysis in which the overall pooled sensitivity of routine EEG (up to 60 minutes recording with the international 10-20 electrode placement system) was 44% and the pooled specificity was 80% (Bouma et al, 2016). An aetiologic factor can be identified in several cases, but in the majority of patients the cause is unknown.

Clinical conditions characterized by transient alteration of consciousness and/or behaviour fall in the differential diagnosis of epilepsy leading to false-positive diagnoses. These diseases include, among others, psychogenic non-epileptic seizures (PNES) that, along with the differing distribution of genetic and environmental risk factors, are possible explanations of the heterogeneous frequency, course and consequences of the disease in the world.

The investigation of the spectrum of epilepsy is the focus of the present thesis. In doing this, I have performed different studies spanning the diagnosis, the outcome and the treatment of the disease. The topics covered include: 1. The differential diagnosis between epilepsy and another common clinical condition (PNES); 2. The verification if epilepsy could be a marker of genetic diseases characterized by intellectual disability and behavioural abnormalities; 3. The

assessment of the long-term outcome of the disease and the identification of different prognostic patterns; 4. The investigation of the dynamic nature of drug-resistant epilepsy (DRE) with reference to the treatments given during the course of the disease. Our findings will be discussed in the context of the available knowledge and a critical appraisal of the frequency and outcome of epilepsy as reported in the literature.

1.1.1. Definitions and terminology

While all people with epilepsy experience seizures, not all individuals with seizures have epilepsy. Epileptic seizures may occur in the context of an acute CNS insult (structural, systemic, toxic or metabolic). These events (provoked or acute symptomatic seizures) are intended as an acute manifestation of the insult and may not recur when the underlying cause has been removed or the acute phase has elapsed (Beghi et al. 2010). According to the International League Against Epilepsy (ILAE), epilepsy is a disease of the brain defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome (Fisher et al, 2014). An unprovoked seizure is a seizure occurring in a person aged one month or older, occurring in the absence of precipitating factors. Unprovoked seizures include events occurring in the absence of a recognized aetiological or risk factor (idiopathic and cryptogenic seizures), in patients with antecedent stable (non-progressing) central nervous system (CNS) insults (remote symptomatic seizures), or in those with progressive CNS abnormalities such as brain tumors, genetic, metabolic or degenerative conditions (progressive symptomatic seizures). Unprovoked seizures may be single or recurrent. Seizures with onset within a restricted area of one hemisphere are classified

as focal (formerly partial), whereas those with onset in both hemispheres are classified as generalized. Different subtypes exist within these two main categories. While terminology has changed over time we will in this chapter keep the terminology used in the original reports when they are cited.

Although epilepsy is, by definition, a chronic clinical condition, patients may achieve seizure remission at variable intervals after the onset of seizures. In epidemiological studies "epilepsy in remission with treatment" is defined by the absence of seizures for at least five years in patients still receiving antiepileptic drugs (AEDs). Epilepsy in remission without treatment (terminal remission) is seizure remission for at least five years in patients off medications at time of ascertainment (ILAE Commission, 1993). These cases represent the inactive epilepsy. By contrast, active epilepsy is defined as being treated with AEDs or having at least one seizure in the preceding 2 or 5 years regardless of treatment (Thurman et al, 2011). The ILAE uses the term "epilepsy resolved" for cases seizure free for ten years of which the last five off medication (Fisher et al., 2014).

1.1.2. Drug-resistant epilepsy

Studies performed in clinical cohorts showed that 30-40% of patients with epilepsy were resistant to the available antiepileptic treatments (Kong et al, 2014; Brodie et al, 2012; Schiller, 2009). In the general population, this percentage seems to be lower, about 15-20% (Sillanpää and Schmist 2006; Berg et al 2012; Picot et al, 2008). This difference can be attributed to selection bias, as in the case of tertiary referral centers for epilepsy, the presence of cases with severe epilepsy syndromes is more frequent. Data from these cases may also reflect the use of different criteria for the definition of drug resistance, the variable number of drugs used, and a different follow-up duration.

Berg and colleagues (2006) proposed a strict definition: 1. Uncontrolled seizures with an average frequency of 1+ per month for at least 2 years; 2. Use of at least 3 different antiepileptic drugs (in monotherapy or in combination); 3. Treatment failure due to lack of control of seizures or withdrawal for adverse reactions. Less strict definitions have also been used, such as those proposed by Arts and colleagues (1999): seizure freedom from at least 3 to 6 months. Accordingly, the prevalence of DRE may vary from 9 to 24% of cases according to the selection criteria used (Berg and Kelly, 2006).

To produce a correct estimate of the prevalence and incidence of drug-resistant epilepsy, representative samples of the general population of patients with epilepsy and a definition shared by the scientific community are needed. The International League Against Epilepsy (ILAE) has recently formulated a new definition of drug-resistance, thus providing a basis for its use in clinical practice. DRE has been considered as having failed at least two well-tolerated and appropriately chosen AEDs, as monotherapy or in combination, to achieve seizure freedom (Kwan et al., 2010). To date, no one study has been performed to assess the actual frequency of drug-resistant epilepsy in well-defined geographic areas.

1.1.3. Psychogenic non-epileptic seizures

PNES are often indistinguishable from epileptic seizures behaviourally, but the EEG recorded during the event does not show epileptiform abnormalities (Benbadis, 2013; Gedzelman and LaRoche, 2015). The physiologic basis of PNES is not well-understood. They are believed to represent an experiential or behavioural response to emotional or social distress leading to temporary loss of control, a form of conversion or somatoform disorder (Reuber, 2008; Reuber, 2009).

The risks, treatments and prognosis of the two diagnoses (epilepsy vs. PNES) differ substantially, so accurate diagnosis is critical to the health and well-being of patients. For example, epileptic seizures (ES) that last > 5 minutes (i.e., status epilepticus) (Trinka et al, 2015) are life-threatening and require immediate emergency treatment. PNES that last > 5 minutes are rarely physically harmful and typically do not require any emergency treatment. Diagnosing true PNES as ES exposes patients to unnecessary treatment with anti-epilepsy medicines. Diagnosing true ES as PNES withholds appropriate treatment, increasing risk of adverse outcomes such as sudden-unexplained death in epilepsy (SUDEP) or other medical complications (Reuber et al, 2004). Recording typical events during inpatient, long-term, video-EEG monitoring (VEM) is the recognized gold-standard method for diagnosis. History, physical examination, events and verbal descriptions observed directly by witnesses are not sufficiently diagnostic if alone, although they do provide valuable clues. However, it is not known whether combining these different characteristics predict diagnosis with sufficient accuracy. One of the aims of this thesis is to test this hypothesis.

Most neurologists consider PNES a complex disorder of psychiatric origin, and, as such, a condition that is not of their competence. However, for at least two decades, cases with PNES have represented up to one third of the patients with refractory seizures admitted to the epilepsy units for diagnostic investigations, in numbers comparable to surgical candidates (Benbadis et al, 2004). These figures have been consistent and epileptologists, constantly facing the differential diagnosis between ES, PNES, and other non-epileptic seizures of non-psychogenic nature, can no longer ignore the condition.

The disorder has been known since the ancient times and appears ubiquitously. Cases with PNES have been described in the industrially developed as well as in the developing countries across ethnicities and cultures (Farghaly et al, 2013; Asadi-Pooya et al, 2013; Alessi and

Valente, 2013; An et al, 2010; Cronje and Pretorium, 2013). The estimated incidence of PNES varies from 1.4 cases per 100,000 per year (about 4% of the incidence of epileptic seizures) according to an Icelandic study (Sidurdardottin and Olaffson, 1998) to 3 cases per 100,000 per year, according to an epidemiological work conducted in Ohio (USA) (Szaflarsky et al, 2000). Since these data are derived from VEM-proven cases followed in specialized neurology centers, such figures are likely to be an underestimate. Three-quarters of patients with PNES are female (Lesser, 1996). The age of onset is "most commonly" between the age of 15 and 25 years, and the disorder is "most commonly" diagnosed between the ages of 25 to 35 years (Reuber et al, 2008). In 20-30% of patients with seizures the nature of the disorder is unrecognized (Smith et al, 1999). The mean delay between the first seizure manifestations and the diagnosis of PNES is about 7-8 years (Reuber et al, 2002; de Timory et al, 2002). A number of patients may also present PNES manifestations after years of epileptic seizures. The mean delay in diagnosing this group (PNES+ES) is 16 years (de Timory et al, 2002). Therefore, epilepsy itself can in fact be regarded as a risk factor for the occurrence of PNES (Reuber et al, 2003). The incidence of PNES associated with ES is unknown.

Despite the alleged "low incidence", the burden of PNES on the individual and society is significant because it affects predominantly young adults in the prime of life and because, when symptoms strike, they are highly disruptive. Two studies found that patients with PNES experience their life as more stressful than patients with epilepsy, also because their coping mechanisms are less effective (Tojek et al, 2000, Frances et al, 1999). The disorder greatly affects productivity. According to a US survey, 69% of 84 patients with PNES were employed at the time their seizure started but only 20% of them still had a job at the time they underwent VEM (Martin et al 2003).

Clinical characteristics of PNES:

The semiology of PNES varies greatly from case to case. According to the predominant manifestations of the attack, the following types of PNES can be identified (Magaudda et al, 2016) :

-*Hypermotor:* with generalized motor phenomena, rhythmic (resembling grand mal seizure) or disordered, like hyperkinetic frontal seizures.

-*Akinetic* (syncope-like if associated with fall): mainly characterized by unresponsiveness without motor phenomena (absence-like), with or without fall.

-*With subjective symptoms*: paraesthesiae, experiential phenomena (visual, acoustic, dejà-vu or vecu, anxiety, fear - without all the features of a panic attack, confusional state).

-*Focal motor like*: with partial clonic or tonic phenomena.

Because of the variety of presentations and the close resemblance of many types of PNES with ES, the distinction between the two conditions may be difficult, at least when based on verbal descriptions by patients or direct witnesses. At close scrutiny, however, differences may become apparent, in certain types of seizures more than others. For instance, the evolving manifestations of an epileptic motor seizure follows a predictable path based on the anatomical organization of the neuronal networks involved by the progression of the ictal discharge. On the contrary, the motor manifestations of PNES follow a different scheme, which lacks anatomical coherence and is tinged with emotional or theatrical features. Nonetheless, it is long known that even the eye of an expert clinician cannot distinguish with certainty a hypermotor frontal lobe seizure from a hypermotor PNES (Saygi et al 1992, Leis et al 1992, Beleza and Pinho 2011). Similarly, episodes of staring and unresponsiveness or drop seizures, although suggeting a psychogenic origin, necessitate documentation by a trained professional or the concomitant EEG to reveal their true nature. Recently, the difficulty of distinguishing PNES with subjective symptoms from parietal lobe ES has been brought to clinical attention (Mc Gonigal et al, 2014).

As said before, the recommended gold standard for a definitive diagnosis is the analysis of the habitual attacks recorded during VEM. This allows direct observation of the semiology of the attack and an assessment of whether the concomitant EEG ("ictal" EEG) shows paroxysmal discharges (epilepsy) or remains normal (PNES). It also allows the recording of ECG, EMG and postictal EEG changes which may be of significance. However, even this approach has its limitations. First of all, in many areas around the world, including Europe, facilities providing VEM are difficult to access or not available. In addition, frontal lobe hypermotor seizures not only closely mimic the semiology of PNES but also often do not show obvious paroxysmal changes in the surface ictal EEG, thus precluding a definite diagnosis (Kanner et al 1990, Saygi et al 1992, Leis et al 1992, Beleza and Pinho 2011). Finally, in a number of cases no events are recorded during the VEM, despite attempts to precipitate the habitual seizures.

When a definitive documentation is lacking, the diagnosis of PNES can be only presumptive, based on historical and clinical data considered to be "typical" of this disorder. There are a number of studies reporting that certain "signs" or "symptoms" are pathognomonic of the disorder as being significantly more frequent in patients with PNES compared to patients with epilepsy. The presence of one or more of such features provides important clues for the differential diagnosis (high sensitivity) although their specificity is often insufficient to establish the diagnosis with certainty (Avbersek and Sisodiya, 2010). Clusters of such "typical" signs have certainly more clout or "weight" than individual signs, but none, so far, has replaced the value of observing the habitual attacks on video with the concomitant EEG. In the study of Syed et al 2011, performed reviewing seizures videos and collecting information through eyewitnesses interviews, a cluster of three signs resulted to be significant for PNES diagnosis, even if eyewitnesses were not so reliable in reporting them. In another study performed using a patient and an observer questionnaire (Reuber et al, 2011), witnesses were more often aware of

seizure triggers and a relationship between PNES and emotional stress than patients. Patients with PNES reported different information from their witnesses and patients with epilepsy about their seizure events, there are more reticent, they describe the event as a space/place they go through (Plug et al, 2009, Rawlings and Reuber 2016). Unfortunatly some signs could not be collected because patients could be completely unaware and unwitnessed during the seizure event. In this cases the use of video is required.

The Nonepileptic Seizures Task Force of the International League Against Epilepsy (ILAE) developed guidelines on standards for the diagnosis of PNES (LaFrance et al, 2013). Minimum requirements for a staged approach to the diagnosis are outlined, based on a review of the literature that include a variety of diagnostic approaches: review of past history, semiology of the attacks, EEG findings, ambulatory EEG findings, results of VEM, neurophysiologic testing, neurohumoral testing, neuroimaging, neuropsychological testing, hypnosis, and conversation analysis. The Task Force, based on the expertize of the participating panel and a compound assessment of data predominantly collected from patients with confirmed diagnosis of PNES, has concluded that *the combination of patient history and direct recording of the attacks on video-EEG is the diagnostic standard*. However, because VEM is not available worldwide, or for some patients events cannot be recorded, the group proposed four categories of PNES diagnosis based on 'degree' of certainty, depending on the available information:

• *Documented PNES* – diagnosis relies on clinical history plus a VEM recording of habitual events ("gold standard").

• *Clinically established PNES* – diagnosis supported by the clinical history, a clinician witness and ambulatory EEG recording of habitual event or events without video. This diagnosis would be appropriate if a clinician witness observed a seizure and documented the symptoms and signs typically found in PNES, such as resistance to eye-opening, or if a clinician could review a non-

EEG event by video or in person.

• *Probable PNES* - this diagnosis is based on clinical history, a clinician review of video recording or witnessing live events, and a normal interictal EEG. This diagnosis would be appropriate if a clinician could review a home or cell phone video recording of seizure activity or witness it in person.

• *Possible PNES* – diagnosis relies on clinical history from the patient or witness and a normal interictal EEG. At minimum, a patient's history and description of events and an eyewitness description could help identify possible PNES, but without the clinician "observing the ictus on video or in person, an alternative diagnosis of epilepsy would have to be considered very carefully."

Even if the VEM of the attacks remains the "gold standard" in all cases, in current clinical settings the diagnosis of PNES may be within reach in other circumstances. For instance, when a health professional can demonstrate the preservation of certain "avoidance" or "self-defense" mechanisms during the patient's apparent state of unconsciousness; or when an experienced professional, reviewing the habitual attacks recorded on video (even a home video) and without concomitant EEG can determine that the single manifestations, or the sequence in which they occur, represent a "physiological" or a "psychological" event. The above evidence would be further reinforced if habitual attacks recorded on ambulatory EEG (without video) were *not* associated with ictal discharges.

Producing such evidence is not free of limitations. Most of all, it requires the presence, and if necessary the intervention, of health professionals familiar with the semiology of both ES and PNES and who could make a reliable judgment on whether there is sufficient proof in favor of one diagnosis or the other.

The diagnosis of PNES must be supported also by the "clinical history" (LaFrance et al, 2013) and it implies a careful survey of antecedent events – remote and recent – as possible aetiological factors, as well as the identification of precipitating factors that may trigger the attacks. To those we may add the specification of individual personality traits and behavioural characteristics that may constitute the facilitating and perpetuating factors. Although the VEM documentation of habitual seizures is usually regarded as the gold standard test confirming the diagnosis, the history-taking is the most important clinical tool in the diagnostic process, needed to define if the events captured by VEM are typical of habitual seizures.

All these observations give rise to interesting speculations regarding the psychophysiology of PNES (Reuber, 2009). Obviously, the appreciation of the multifactorial complexity of the aetiology of PNES is essential to institute effective therapeutic strategies.

Contrary to epilepsy that can be either transmitted genetically (*primary/idiopathic epilepsy*) or acquired secondarily to a brain injury (*secondary/symptomatic epilepsy*), PNES appears to be an exclusively acquired disorder. It is reasonable to assume that at the origin there is a distant or recent traumatic experience that, combined with environmental factors and a characteristic psychological and personality profile, leads to the manifestations of PNES.

Approximately 90% of patients with PNES report significant traumatic experiences in the past (Fiszmann et al, 2004). Such "injuries", mostly of psychological nature, seem to be less important aetiological factors in men (Oto et al, 2005), in those with a late onset of the attacks (Duncun et al, 2006), and those with learning difficulties (Duncun et al, 2008). Traumatic events can occur in adults and can be "physical" (see: war veterans (Dwortzky et al, 2005) or victims of rape) or "work-related" (e.g.the loss of the job in a successful adult male). Presumably, they all represent a shattering experience that deeply destabilizes the individual. The results of Alper et al 1993, support the impression that childhood abuse is more common among patients with

conversion NES than with epilepsy, and suggest that in some cases childhood abuse may be a contributory pathogenic factor.

As summarized in the review by Reuber (Reuber, 2008), trauma is present in the history of 32.4% to 88% of patients with PNES compared to 8.6% to 37% in the history of patients with epilepsy. Sexual abuse was more represented (24% vs. 7.1%) than physical abuse (15.5% vs. 2.9%). Thus, history of abuse is significantly more frequent in PNES than epilepsy. These figures are probably an underestimate considering that many patients may be reluctant to admit and discuss past events of such intimate nature, particularly in certain cultures. It is apparent from these data and from the experience of those familiar with this condition that sexual abuse is a frequent, although not necessarily a mandatory component in the pathogenesis of PNES. The role of trauma in the pathophysiology of PNES has been studied closely by Hingray (Hingray et al, 2011). Patients with history of trauma have at least one psychiatric comorbidity or antecedent and a higher median score for dissociative mechanisms ($p<0.001$). No patient in the no-trauma group had a history of psychiatric comorbidity or current psychiatric disorders. Patients without history of trauma, besides absence of psychiatric comorbidity, report more frequently "frustration situations" as triggering factors of PNES and subsequent *sick leaves* as perpetuating factors ($p=0.001$).

Such information suggests that exploring the psychological risk factors and the psychiatric comorbidities are just as important for the differential diagnosis as the analysis of the semiology of the attacks.

1.2 Epidemiology of epilepsy

1.2.1. Incidence

The worldwide annual incidence of epilepsy from 24 to 190 per 100,000. The overall incidence of epilepsy in high income countries ranges from 24 and 71.0 per 100,000 per year (Table 1.1). In low/middle income countries the incidence of the disease is higher (Table 1.2) and is up to 190 per 100,000.

1.2.2. Prevalence

The overall prevalence of epilepsy ranges from 2.7 to 105 per 1,000 population, although in the majority of the published reports the rate of active epilepsy varied from 4 to 8 per 1,000. The prevalence of active epilepsy is generally lower in high income countries (Table 1.3) than in low/middle income countries (Table 1.4), which may reflect a lower prevalence of selected risk factors (mostly infection and trauma), a more stringent case verification, and the exclusion of isolated provoked and unprovoked seizures. In a systematic review and meta-analysis of 197 prevalence studies, the point prevalence of active epilepsy was 6.4 per 1,000 (95%CI 5.6-7.3) and the lifetime prevalence was 7.6 per 1,000 (95%CI 6.2-9.4) (Fiest et al, 2017). The prevalence was lowest in infancy and tended to increase with age, with a peak at 20-29 years and a subsequent decrease. Both lifetime and active period prevalence were higher in low/middle income countries than in high income countries, but the difference for active epilepsy was not significant. These differences can be mostly explained by the differing distribution of the risk factors and the shorter life expectancy in the latter.

As with incidence, the prevalence of epilepsy tends to prevail in men (Fiest et al, 2017). However, this finding is not consistent across studies and, with few exceptions, is not statistically significant. In multiracial populations, the lifetime prevalence of epilepsy is more

prevalent in blacks than in whites (7.5 vs. 5.9 per 1,000) but, among whites, the prevalence was higher in Hispanics than in non-Hispanics (7.5 vs. 4.7 per 1,000) (Kelvin et al, 2007). Ethnic and racial differences and different socio-cultural environments may explain the heterogeneity of the figures.

Focal seizures are commoner than generalized seizures both in children and adults. In prevalence studies in adults from high income countries, focal seizures were reported in 55-60% of cases, generalized seizures in 26-32%, and unclassifiable seizures in 8-17%. Different figures are present for children (36-66%, 30-62%, and 2-4%), mostly depending on a different distribution of epilepsy syndromes, and for low/middle-income countries (11-55%, 26-86%, and 0-19% respectively), as a consequence of a less accurate diagnostic ascertainment of minor seizures (other than generalized tonic-clonic) (Forsgren, 2004).

The prevalence of epilepsy types has been mostly studied in children and adolescents from Baltic and Scandinavian countries (Forsgren, 2004). In Estonia, the prevalence of idiopathic epilepsies in children was 1.2 per 1,000, and that of cryptogenic epilepsies was 1.0 per 1,000. In Lithuania, focal epilepsies in children were the commonest syndromic category (2.3 per 1,000) followed by generalized epilepsies (1.3 per 1,000) and undetermined epilepsies (0.6 per 1,000). Focal epilepsies were the predominant syndromic category in 41-54% of cases from Sweden, Finland and Norway, followed by generalized (37-48%) and unclassified (5-10%). In these countries, idiopathic partial epilepsy with centro-temporal spikes was 5-17%, absence epilepsy 6-8%, juvenile myoclonic epilepsy 1-5%, West syndrome 0.5-8%, and Lennox-Gastaut syndrome 2-6%.

Socio-economic background affects the frequency of epilepsy both in high income and in low/middle income countries (Beghi & Hesdorffer, 2014). A strong correlation was detected

between the prevalence of epilepsy and social deprivation, defined by unemployment, no car in the household, overcrowded households, and households not occupied by the owner.

1.3 Prognosis of epilepsy

The overall prognosis of epilepsy is favorable in most patients. Reports from several low/middle income countries (where patients with epilepsy are largely untreated) give prevalence and remission rates overlapping to those of high income countries (Beghi et al, 2015). As in most low/middle income countries the incidence of epilepsy is higher than in high-income countries and increased mortality may explain only in part the difference between incidence and prevalence, spontaneous remission of seizures is a likely explanation. In addition, contrary to the old reports, studies done in the last 30 years in newly diagnosed patients have consistently shown that 55-68% of cases tend to achieve prolonged seizure remission (Table 1.5). However, in a long-term population-based study done in patients with childhood-onset epilepsy, different remission patterns were seen. Half of the patients entered terminal remission, without relapse and one fifth after relapse. One third had a poor outcome in terms of persistent seizures after remission or without any remission (Sillanpaa & Schmidt, 2006). These patterns have been confirmed in part by others (Brodie et al, 2012; Shorvon & Goodridge, 2013; Berg & Rychlik, 2015; Giussani et al, 2016).

The risk of relapse after a first unprovoked seizure range from 23 to 71% (Beghi, 2003). Population-based studies provided more homogeneous relapse rates at one (36-37%) and two years (43-45%). In a systematic review of 16 reports, the average recurrence risk was 51% (95% CI 49-53%) (Berg & Shinnar, 1991). After a first unprovoked seizure, the probability of a relapse decreases with time. 50% of seizure relapses occur of recurrences occur within 6 months from the initial seizure and 76-96% within 2 years. A documented aetiology of the seizure and an abnormal EEG pattern are the two most consistent predictors of recurrence. The pooled two-

year recurrence risk is lowest for an idiopathic or cryptogenic first seizure with a normal EEG (24%; 95% CI 19-29%), intermediate for a remote symptomatic seizure (48%; 95% CI 34-62%) with normal EEG *or* an idiopathic/cryptogenic seizure with an abnormal EEG (48%; 95% CI 40-55%), and highest with a remote symptomatic seizure with an abnormal EEG (65%; 95% CI 55-76%) (Berg & Shinnar, 1991). Interictal EEG epileptiform abnormalities tend to be associated with a higher risk of seizure recurrence than non-epileptiform abnormalities. Seizures occurring during sleep are associated with a higher risk of recurrence both in children and in adults. Focal seizures are also correlated with a higher risk of recurrent seizures, even after controlling for etiology and EEG abnormalities. A positive correlation between seizure relapse and family history of seizures has been confirmed in patients with idiopathic or cryptogenic first seizures. History of acute symptomatic seizures prior to the first unprovoked seizure has been occasionally found to increase the risk of relapse, while evidence is inconclusive or lacking for sex, age, and status epilepticus.

The prognosis of untreated epilepsy can be assessed only in low income countries where epilepsy is largely untreated (treatment gap ranging from 70 to 94%) (Mbuba et al, 2008). In a population-based study done in Ecuador the cumulative annual incidence rate was 190 per 100,000 and the prevalence rate of active epilepsy was 7 per 1,000, which implies a remission rate of at least 50% (Placencia et al, 1992). Similar prevalence rates of active epilepsy were found in other countries (Watts, 1992; Nicoletti et al, 2009). These findings lend support to the hypothesis that spontaneous remission of epilepsy is a common event.

Generally, treatment started when at least two unprovoked seizures have occurred. After a second unprovoked seizure, the risk of a third seizure has been estimated as 73% and, among those with a third unprovoked seizure, the risk of a fourth as 76% (Hauser et al, 1998). Population-based studies on the long-term prognosis of treated epilepsy report a 58-65%

cumulative 5-year remission rate at 10 years (Table 1.5). This number rises to about 70% by 20 years following seizure onset.

Aetiology of epilepsy is by far the strongest prognostic predictor for seizure recurrence in patients with epilepsy. Genetic (formally idiopathic) epilepsy has a better chance of seizure remission than structural, infectious, metabolic, immune (ex-symptomatic) or unknown (ex-cryptogenic) epilepsy (Schaffer et al, 2017). In the Rochester, Minnesota, symptomatic epilepsies had a significantly lower chance of 5-year remission compared to idiopathic epilepsies (30 vs. 42% at 15 years), patients with congenital neurological dysfunction have the lowest chance to reach seizure remission (Annegers et al, 1979). Lower remission rates in patients with symptomatic epilepsies were found in several European countries (Beghi et al, 2015). Other indicators of 5-year remission in the Rochesterstudy included absence of EEG epileptiform abnormalities (OR 1.6) and absence of generalized tonic-clonic seizures. In the National General Practice Study of Epilepsy (NGPSE) in the UK, the number of seizures after the first seizure was the only independent predictor of 1- and 2-year remission (MacDonald et al, 2000).

Sander (1993) proposed four different prognostic groups: 1. Excellent prognosis (~20-30% of the total) with high probability of spontaneous remission (benign focal epilepsies, benign myoclonic epilepsy in infancy, and epilepsies provoked by specific modes of activation, i.e. reflex epilepsies); 2. Good prognosis (~ 30-40%) with easy pharmacological control and possibility of spontaneous remission(childhood absence epilepsy, and some focal epilepsies); 3. Uncertain prognosis (~ 10-20%), which may respond to drugs, but tend to relapse after treatment withdrawal (juvenile myoclonic epilepsy, and most partial symptomatic or cryptogenic epilepsies); 4. Poor prognosis (~ 20%) in which seizures tend to recur despite intensive treatment

(epilepsies associated with congenital neurological defects, progressive neurological disorders, and some symptomatic or cryptogenic partial epilepsies).

1.3.1. Mortality of epilepsy

The mortality rate of epilepsy ranges from 1 to 8 per 100,000 population per year, but international vital statistics give annual mortality rates of 1-2 per 100,000 (Gaitatzis & Sander, 2004).

Based on population-based studies investigating mortality in high income countries, the standardized mortality ratio (SMR) for incident unprovoked seizures or epilepsy was found to range from 1.6 to 3.0 (Thurman et al, 2016). In prospective and retrospective incidence cohorts, the SMR for epilepsy ranges from 1.6 to 5.3 in children and adults (Table 1.6). The SMR is generally higher among children, due to lower mortality rates in the general population, and also higher during the first years after diagnosis (Thurman et al., 2017). In low/middle income countries (Table 1.7), the annual mortality rate in people with epilepsy is higher than in high income countries and ranges from 9.7-45.1 deaths per 1,000, with a median of 2.6 (range 1.3-7.2) (Levira et al, 2017). Median SMRs are slightly higher in men than in women (SMR 5.0 vs. 4.5) and relatively higher SMRs in children and adolescents, patients with symptomatic epilepsies, and those reporting less adherence to treatment.

1.4 Aetiology of epilepsy

Comorbidities in epilepsy represent an important burden (Keezer et al 2016). Several somatic and psychiatric comorbidities tend to prevail significantly in people with epilepsy when compared to the general population (Gaitatzis et al, 2012; LaFrance et al, 2008). Several mechanisms can explain the association between epilepsy and a number of comorbidities,

including causal relation, shared risk factors and bidirectional effects. Factors clearly associated with the development of epilepsy must be identified before accepting the concept of a causal association between a brain insult and the occurrence of epileptic seizures. First, the timing of the seizure(s) must be identified, to separate acute symptomatic from unprovoked seizures. Second, the frequency and spectrum of epilepsy and putative aetiological factors in the general population must be assessed to define the fraction of epilepsies associated to a given risk factor and the risk of epilepsy attributable to that factor. Third, the accuracy and validity of the diagnostic process must be considered. Fourth, evidence of a causal relationship should be produced to exclude the possibility of a chance association even at the presence of a well-established aetiological factor. This requires the satisfaction of specific criteria, including temporal sequence, strength and consistency of association, biological gradient and plausibility. The ILAE proposes classification into six different categories: structural, genetic, infectious, metabolic, immune, as well as an unknown aetiological group (Scheffer et al, 2017).

In incidence studies, the proportion of cases with documented aetiology has been reported to vary from 13.7% in Ethiopia to 51.6% in Poland (Beghi, 2004). The differences are mostly explained by the structure of the population at risk, the prevalence of the aetiological factors in the local environment, the study design, and the extent of the diagnostic process to identify etiologies. In the Rochester, Minnesota population (where the majority of cases were included before the era of modern neuroradiology), epilepsy was idiopathic/cryptogenic in about two-thirds of patients. The commonest aetiological factors included cerebrovascular disease (10.9%), congenital neurological disorders (8.0%), trauma (5.5%), neoplasm (4.1%), degenerative disorders (3.5%), and infection (2.5%) (Hauser et al, 1993). Aetiological factors varied significantly with age, congenital disorders being most common in children aged less than 14 years and cerebrovascular disorders in the elderly.

To some part, the risk of epilepsy is accounted for by genetic factors. Despite the increasing pace of gene discovery in the epilepsies, the contribution of specific genes still needs to be elucidated. In epidemiology, the role of the genetic components has been mostly explored by studies of familial aggregation of epilepsy, studies on paternal and maternal transmission, and twin studies. However, these studies often suffer from methodological limitations including referral and reporting biases, small sample size, ambiguous disease definition, and lack of controls (Hauser & Hesdorffer, 1990). Siblings and offspring of patients with epilepsy have a two- to threefold increased risk to develop epilepsy. In offspring of patients with epilepsy, the cumulative incidence of unprovoked seizures at age 25 is about 6%, as opposed to 1-2% of the general population (Hauser & Hesdorffer, 1990). The risk of seizures among offspring of mothers with epilepsy exceeds that of offspring of fathers with epilepsy. If a proband has an early age at onset of seizures, there is an increased risk of seizures among siblings and offspring. The risk of unprovoked seizures is highest among siblings of probands with generalized epilepsy and is related to seizure type (mostly tonic-clonic or absence) and EEG abnormalities (mostly generalized spike and slow wave patterns). In the only comprehensive study in first-degree relatives of probands with epilepsy (Peljto et al, 2014), the cumulative incidence of the disease to age 40 years was 4.7%, accounting for a three-fold increased risk (measured by the standardized incidence ratio, SIR) compared to the general population. A significantly increased risk was found for idiopathic generalized epilepsy (SIR 5.0; 95%CI 3.2-7.4), generalized epilepsy due to structural-metabolic causes (SIR 3.9; 95%CI 1.0-8.2) and focal epilepsy (SIR 4.8; 95%CI 1.6-9.9). A five-fold increased incidence of epilepsy was found in the offspring of female probands, restricted to focal epilepsy. The results of this and other epidemiological studies providing heritability estimates support the concept that epilepsy has a robust genetic component.

Although the role of pre- and perinatal risk factors in the etiology of epilepsy seems established, most of the studies provide inconsistent findings and indicate, at best, a moderate association. These results may be explained by the use of differing definitions of pre- and perinatal factors, the study populations, the methods of ascertainment of the cause-effect relationship, and the sample size.

Mental retardation and cerebral palsy are markers of brain dysfunction, which explains the significant association with epilepsy. In a systematic review of 38 studies, the pooled prevalence among people with intellectual disabilities was 22.2% (95%CI 19.6-25.1) with increase with the disability level (Robertson et al, 2015). In the U.S. National Collaborative Perinatal Project, a study following newborns prospectively up to age 7, epilepsy occurred in 34% of children with cerebral palsy and it was present in 19% of children developing epilepsy (Nelson & Ellenberg, 1987). In this cohort, the risk of mental retardation was 5.5 times higher among children developing epilepsy a after febrile seizure than in children with a febrile seizure alone. Epilepsy was more common in individuals with severe/profound mental retardation compared to mild/moderate mental retardation (Hauser & Hesdorffer, 1990).

1.4.1 Epilepsy and multiple disabilities

About 30% of patients evaluated for epilepsy are disabled (Genton et al 1996).

Disabilities associated with epilepsy include neurological and/or sensory dysfunction, mental retardation, psychiatric and/or behavioural problems. Several aetiological factors have been described causing the association between epilepsy and disability (Genton 1996). The frequency of epilepsy in these patients is directly proportional to the severity of the mental disability (Hagberg and Kyllerman, 1983; Corbett J, 1985; 79-89; Salbreux et al, 1979; Col 1981) and in institutionalized patients (Iivanianen et al 1985; Mariani et al, 1986).

Focusing on the prevalence of epilepsy as function of aetiology in disability, prenatal encephalopathies are less epileptogenic than perinatal and postnatal (Iivanainen 1985, Ingram 1964). Epilepsy is a common condition in prenatal encephalopathies caused by genetic syndromes, like Fragile-X (Fra-X) syndrome (25-40%), tuberous sclerosis (70%), Sturge-Weber (80%), Rett Syndrome (72%), Aicardi syndrome (100%), Angelman syndrome (90%). Another syndrome in which epilepsy is recurrent (exceeding 75% of cases) is the 15q11-13 duplication syndrome (idic(15)) (Battaglia, 2008), a rare syndrome characterized by an unspecific phenotype, clinical heterogeneity and a wide spectrum of severity, and for which no formal characterisation has been attempted. The incidence is estimated to be 1 per 30,000 live births with a sex ratio of 1:1 (Schinzel and Niedrist, 2001).

In this thesis I focus on this genetic syndrome as an example in order to validate the diagnosis of a genetic epilepsy syndrome characterized by intellectual disability and abnormal behaviour. The aim was to detect a cluster of signs and symptoms, laboratory and instrumental tests useful to discriminate this condition from the diseases that fall in the differential diagnosis (other neurodevelopmental disorders with mental retardation, intellectual disability, epilepsy and altered behaviour) and understand if epilepsy could be used as a marker of the disease.

Table 1.1. Incidence (per 100,000 per year) of epilepsy in high income countries.

Author, year	Country (§)	Age	Incidence rates	Notes
Camfield, 1996	Canada	Children	46.0	
Christensen, 2007	Denmark	All ages	68.8	
Beilmann, 1999; Oun, 2003	Estonia	All ages	35.4-45.0	
Gaily, 2016; Saarinen, 2016; Keranen, 1989; Sillanpaa, 1998; Sillanpaa 2006	Finland	All ages	24.0-124.0	Higher rates in infants
Freitag, 2001	Germany	Children	60.3	
Olaffson, 1996; Olaffson, 2005	Iceland	All ages	33.3-46.5	
Loiseau, 1990	France	All ages		
Cesnik, 2013; Casetta, 2012; Giussani, 2014; Granieri, 1983	Italy	All ages	32.5-57.0	Higher rates in children
Nakano, 2014	Japan	All ages	24-53	Higher rates in older ages
De Graaf, 1974; Breivik, 2008	Norway	All ages	32.8-46.8	Higher rates in children
Pavlovic, 1998	Serbia	Children	650.0	Cumulative incidence
Forsgren, 1996; Brorson, 1987	Sweden	All ages	50.0-56.0	

Jallo, 1997	Switzerland	All ages	71.0	
MacDonald, 2000; Eltze, 2013	United Kingdom	All ages	46.0-70.1	Higher rates in infants
Hauser, 1993; Holden, 2005; Zarrelli, 1999; Hauser, 1993	United States	All ages	35.0-71.0	Higher rates in administrative data
Joensen, 1986	Faroe Islands	All ages	42.0	
Kotsopoulos, 2005	The Netherlands	>13 years old	29.5	

Table 1.2. Incidence (per 100,000 per year) of epilepsy in low/middle income countries.

Author, Year	Country (§)	Age	Incidence rates	Notes
Debouverie, 1993	Burkina-Faso	All ages	83.0	
Lavados, 1992	Chile	All ages	113.0	
Placencia, 1992	Ecuador	All ages	122.0-190.0	Urban and rural area; reasons for this difference not identified
Tekle-Heimanot, 1997	Ethiopia	All ages	64.0	
Mani, 1998	India	All ages	49.3	
Winkler, 2009	Tanzania	All ages	81.1	
Kaiser, 1998	Uganda	All ages	215.0	
Li, 1985	China	All ages	35.0	
Ibinda, 2014; Mung'ala-Odera, 2008	Kenya	All ages	39.16-187.0	Lower rates in women and higher rates in children
El Tallawy, 2010	Egypt	All ages	43.14	
Houinato, 2013	Benin	All ages	10.5	
Jallon, 1999	Martinique	All ages	64.1	

Ba-Diop, 2014	Sub-Saharan Africa	All ages	81.7
Burneo, 2005	Latin America	All ages	77.7-190
Medina, 2005	Honduras	All ages	92.7
Dogui, 2003	Tunisia	Children	102.1

Table 1.3. Prevalence (per 1,000) of active epilepsy in high income countries.

Author, year	Country (§)	Age	Prevalence ratios	Notes
D'Souza, 2012	Australia	All ages	4.4	
Christensen, 2007	Denmark	All ages	6.0	
Beilmann, 1999; Oun, 2003	Estonia	All ages	3.6-5.3	Lower ratios in children and higher in adults
Picot, 2008	France	Adults	5.4	
Sillanpaa 1973;Keranen, 1989; Eriksson, 1997	Finland	All ages	3.2-6.3	Lower ratios in children
Olaffson, 1999	Iceland	All ages	4.8	
Gallitto, 2005; Cossu, 2012; Giussani, 2015; Giussani, 2016; Granieri, 1983	Italy	All ages	3.0*-7.9	*Aeolian Islands
Nakano, 2014; Oka, 2006	Japan	All ages	2.7-40.0	Lower ratios in children and higher in older ages
Waaler, 2000;Syvertsen, 2015	Norway	All ages	5.1-6.5	Lower ratios in children
Bilikiewicz, 1988	Poland	>16 years	3.7	
Luengo, 2001, Benavente, 2009; Garcia-Martin, 2012	Spain	All ages	4.1-6.3	Higher ratios in adolescents
Brorson, 1987; Forsgren, 1992; Sidenvall, 1996; Bolin, 2015	Sweden	All ages	4.2-8.8	Lower ratios in children
De La Court, 1996	The Netherlands	Adults and elderly	9.0	
Goodridge, 1983; Wallace,	United Kingdom	All ages	4.0-8.0	

1998; MacDonald, 2000; Wright, 2000; Gaitatzis, 2004; Steer, 2014				
Hauser, 1991; Kobau, 2004; Holden, 2005; Chong, 2013; Ablah, 2014	United States	All ages	7.2*-21.0	*Only adults in Georgia and in Tennessee
Chen, 2006; Hsie, 2008	Taiwan	All ages	2.7*-4.2	Lower ratios in adults
Tellez-Zenteno, 2004; Prasad, 2011; Schiariti, 2009	Canada	All ages	4.03-5.5	
Al Rajeh, 2001	Saudi Arabia	All ages	6.5	
Josipovich-Jelic, 2011	Croatia	All ages	10.9	
Joensen, 1986	Faroe Islands	All ages	7.6	
Endziniene, 1997	Lithuania	Children	4.2	
Kruja, 2012	Albania	All ages	14.2	
Pavlovic, 1998	Serbia	Children	6.5	

Table 1.4. Prevalence (per 1,000) of active epilepsy in low-middle income countries

Author, year	Country (§)	Age	Prevalence ratios	Notes
Nicoletti, 1999	Bolivia	All ages	11.1	
Lavados, 1992	Chile	All ages	17.7	
Placencia, 1992; Cruz, 1999; Del Brutto 2005	Ecuador	All ages	6.7-22.62	Higher ratios in migrant populations
Tekle-Heimanot, 1990	Ethiopia	All ages	5.2-29.46	Higher ratios in the Zay society after a door-to-door survey
Radhakrishnan, 2000; Banerjee, 2009; Pandey, 2014	India	All ages	4.9-7.0	Higher ratios in children
Aziz, 1997; Malik, 2011	Pakistan	All ages	7.0-9.98	
Gracia, 1990	Panama	All ages	22.0-57.0	Lower ratios in Panama City populations than in the Caribbean Coast
Dent, 2005; Winkler, 2009; Hunter, 2012	Tanzania	All ages	2.91-8.7	Lower ratios in adults and higher in a door-to door survey
Attia-Romdhane, 1993	Tunisia	All ages	4.0	
Marino, 1987; Gomes, 2002; Borges, 2004	Brazil	All ages	5.1-8.2 active 13.0 lifetime	
Gomez, 1978; Pradilla, 2003; Velez, 2006	Colombia	All ages	10.3 active 19.5 lifetime	
Li, 1985; Kwong, 2001; Wang, 2003; Fong, 2008;	China	All ages	1.52 – 4.4 active 23.5 lifetime	Lower ratios in adults with active convulsive epilepsy

Zhao, 2010; Hu, 2014; Pi, 2014				
Mendizabal, 1996; Garcia-Noval, 2001	Guatemala	All ages	5.8-18.0*	Higher ratios in two rural Guatemalan communities
Sridharan, 1986	Libya	All ages	2.3	
Lee, 2012	Korea	All ages	2.41	
Aziz, 1997; Karaagac, 1999; Onal, 2002; Aydin, 2002; Huseynoglu, 2012; Velioglu, 2010; Canpolat, 2014; Ozkan, 2015	Turkey	All ages	2.5-8.6	Lower ratios in adolescents and higher rates in children
El Tallawy, 2010; Farghaly, 2013	Egypt	All ages	2.1-6.9	Lower ratios in adults
Ebrahimi, 2012	Iran	All ages	7.9	
Lomidze, 2012	Georgia	All ages	8.8	
Gonzales, 2015	Peru	Adults	15.3-25.0-35.6	Lower ratios in the urban group, middle ratios in the rural group, higher ratios in migrant group.
Mung'ala-Odera, 2008; Ibinda, 2014	Kenya	All ages	2.59-11.0	Lower ratios in active convulsive epilepsy, higher ratios in children
Wagner, 2014	South Africa	All ages	7.0	
Osakwe, 2014	Nigeria	All ages	4.7-20.8	Lower ratios in the rural community and higher ratios in

				the semi-rural community
Ngugi, 2013; Ba-Diop, 2014	Sub-Saharan Africa	All ages	7.0-14.8	
Ndoye, 2005	Senegal	All ages	14.2	
Preux, 2011	Cambodia	All ages	5.8	
Yemadje, 2012; Houinato, 2013	Benin	All ages	8.2-12.7*	* Capture-recapture method in rural community Lower ratios in ≥15 years
Nitiema, 2012	Burkina Faso	All ages	45.0	Lifetime
Magalov, 2012	Azerbaijan	All ages	9.02	
Coleman, 2002	Gambia	All ages	4.9	Lifetime
Burneo, 2005	Latin America	All ages	6.0-43.2	Lifetime
Birbeck, 2004	Zambia	All ages	12.5	
Balogou, 2007	Togo	All ages	15.7	
Rajbhandari, 2004	Nepal	All ages	7.3	
Medina, 2005	Honduras	All ages	15.4	
	Cameroon	All ages	104.97	

Table 1.5. Population-based longitudinal studies on the remission rates in epilepsy

Author, year	**Country (§)**	**Age**	**Follow-up time, years**	**%(duration) remission**
Sillanpaa, 2014	Finland	Children	45	61% (5-yr)
MacDonald, 2000; Lhatoo, 2001; Cockerell, 1995; Cockerell, 1997;	United Kingdom	All ages	Up to 12	95% (1-yr) 86% (3-yr) up to 71% (5-yr) 54% (5-yr terminal)
Annegers, 1979; Berg, 2015	United States	All ages	Up to 20	76% (5-yr) In children 95% (1-yr), 92% (2-yr), 89% (3-yr), 81% (5-yr)
Wakamoto, 2000	Japan	Children	19	62.8% (5-yr)
Jonsson, 2011	Sweden	All ages	10	In children 75.6% In adults 68 % (1-yr),64% (3-yr), 58% (5-yr)
Geerts, 2010	Holland	Children	15	71% (5-yr terminal)
Camfield, 2005	Canada	Children	8	71% (3-yr)
Okuma, 1981	Japan	All ages	3-10	56, 59 and 62 % (terminal remission)
Nicoletti, 2009	Bolivia	All ages	10	43.7% (5-yr)
Houinato, 2013	Benin	All ages	18 months	45% (total seizure remission)
Placencia, 1992	Ecuador	All ages	4	21% (terminal remission)

Table 1.6. Community-based studies of mortality in epilepsy in high-income countries

Author, year	Country (§)	Age	Mortality measures	Notes
Camfield, 2002	Canada	Children	SMR 7.5	
Sillanpaa 2013; Nevalainen, 2013	Finland	All ages	SMR 6.4* HR 3.21	*Children
Rakitin, 2011	Estonia	Adults	SMR 2.6	
Holst, 2013	Denmark	< 35 years old	HR 11.9	
Olafsson, 1998; Rafnsoon, 2001	Iceland	All ages	SMR 1.6 W 0.79 M 2.25	
Zielinsky, 1974	Poland	All ages	SMR 1.8	
Nilsson, 1997; Lindsten, 2000	Sweden	All ages	SMR 2.5-3.6*	*≥15 years old
Cockerell, 1997; Lhatoo, 2001; Morgan, 2002; Neligan, 2011	United Kingdom	All ages	SMR 2.1-3.0	
Hauser, 1980; Berg, 2004; Benn, 2008; Nickels, 2012	United States	All ages	SMR 1.7-7.54*	Children

Table 1.7. Community-based studies of mortality in epilepsy in low-middle income countries

Author, year	Country (§)	Population	Mortality measures	Notes
Nicoletti, 2009	Bolivia	All ages	SMR 1.34	
Mu, 2011; Ding, 2013	China	All ages	SMR 2.9-4.9	Lower ratios in a follow-up survey and higher rates in a prospective study
Ngugi, 2014	Kenya	All ages	SMR 6.5	
Houinato, 2013	Benin	All ages	Mortality rate 22.2 per 1,000	
Kochen, 2007	Argentina	All ages	SMR 2.45	
Kaiser, 2007	Uganda	All ages	SMR 7.2	
Carpio, 2005; Banerjee, 2010	India	All ages	SMR 0.76-2.58*	Lower ratio in a postal and telephone survey among the Parsi community and higher ratio in a two-stage door-to-door survey of a stratified random sample in Kolkata
Kamgno, 2003	Cameroon	All ages	Mortality rate 28.9 per 1,000	
Carpio, 2005	Mali	All ages	Mortality rate 34.9 per 1,000	
Tsai, 2005	Taiwan	All ages	Mortality rate 0.8 per 100,000	
Carpio, 2005	Ecuador	All ages	SMR 6.3	
Carpio, 2005	Martinique	All ages	SMR 4.25	

1.5 Aims of the PhD thesis

As indicated above, epilepsy is a chronic clinical condition affecting both sexes and all ages with worldwide distribution; the disease can be also defined as a symptom complex arising from a number of disordered brain functions, which may be secondary to a variety of pathologic phenomena. The heterogeneity of the epilepsies, some of them rare and/or difficult to ascertain, raise a number of unsolved problems.

Open questions include, among others:

- Still about one-third of patients seen in epilepsy centers have non-epileptic attacks, most of which of psychogenic origin; the early identification of these attacks is still a matter of debate;
- For several clinical conditions characterized by epilepsy associated with intellectual disability and abnormal behavior, there is a virtual lack of clinical diagnostic criteria as the phenotype is fairly unspecific;
- The distribution of DRE and the prognostic patterns in well-defined population-based samples are still ill-defined.

The ultimate aim of my thesis is to contribute to a better definition of the phenotype of epilepsy by helping to exclude diseases that could fall in the differential diagnosis (e.g. PNES), predicting the diagnosis of an epileptic syndrome based on an accurate assessment of the phenotype, and investigating the outcome of the disease in relation to the response to the available treatments along different pathways:

1-using epilepsy as marker of disease;

2- analyzing the response to treatment as a marker of the prognosis of the disease;

3- using samples representative of the general population.

To fulfill this aim, I worked on three subprojects:

1. The study of the phenotypes of non-epileptic seizures of psychogenic origin.

2. The validity of the diagnosis of INV-Dup 15, a rare genetic epilepsy syndrome with a non-specific phenotype;

3. The assessment of the prevalence, incidence, the long-term prognosis and treatment response of DRE in a well-defined population.

2. Introducing the characterisation studies

The first two projects presented in the next two sections of my thesis consist of two studies on the characterisation of two different conditions:

- The first is PNES, a borderline condition between neurology and psychiatry with greatly variable manifestations that often resemble those of epileptic seizures.
- The second is a genetic syndrome with an unspecific phenotype in which epilepsy is a common clinical feature, idic(15) syndrome;

The aim of these two studies is to characterise the diagnosis of PNES and idic(15) syndrome without the gold standard diagnostic instruments, that are respectively the VEM (PNES) and the genetic analysis (idic(15)) and to identify clinical signs and symptoms able to discriminate with high specificity and sensitivity these two different conditions.

Previous reports, that are part of my PhD program, have been completed in the framework of the PNES MI-RO project:

- Erba G, Bianchi E, Giussani G, Langfitt J, Juersivich A, Beghi E. A new patient-oriented questionnaire for differentiating epileptic from psychogenic non-epileptic seizures. Value, limitations, future directions. JNNP 2017 (submitted).

- Beghi M, Erba G, Cornaggia CM, Giussani G, Bianchi E, Porro G, Russo M, Beghi E. Engaging Psychiatrists in the diagnosis of PNES. What can they contribute? Seizure 2017 (submitted).

- Erba G, Beghi E, Magaudda A, Bianchi E, Giussani G, Di Rosa G, Laganà A, Chiesa V, Juersivich A, Langfitt J. In response: Towards a quantitative assessment of psychogenic nonepileptic seizures. Epilepsia,2016;57:1011-2.

-Erba G, Giussani G, Juersivich A, Magaudda A, Chiesa V, Laganà A, Di Rosa G, Bianchi E, Langfitt J, Beghi E. The semiology of psychogenic nonepileptic seizures revisited: Can video alone predict the diagnosis? Preliminary data from a prospective feasibility study. Epilepsia, 2016;57:777-85.

3. The MI-RO PNES Project

Abstract

The first aim of this study was to investigate if, when and to what extent, a paroxysmal event captured on video and interpreted by epileptologists could contribute to the differential diagnosis without EEG. This information would be particularly relevant when the EEG is not available or in case clinicians may elect to screen the events of patients with mixed seizure disorders on video before referral to a monitoring unit. Five neurologists were asked to review 23 videos of seizures events of 21 unselected consecutive patients admitted for video-EEG monitoring (VEM). They were asked to rate the videos for quality and content, and to choose the correct diagnosis among epileptic seizures (ES); PNES; Other nonepileptic seizures (NES); "Cannot Say". They were also requested to explain in their words the reasons they considered to reach the diagnosis. In about 1/3 of cases, a confident diagnosis of PNES/ES based on the analysis of video data alone can be established. Our results benefit all affected patients, particularly those with no access to VEM units.

The second aim was to verify if four psychiatrists blinded to the diagnosis could predict the diagnosis of psychogenic non-epileptic seizures (PNES) by reviewing videos of seizures of various types and to compare the accuracy and the criteria leading to the diagnosis by the psychiatrists with those used by epileptologists, using the same methodology. Psychiatrists were

found to be less accurate than neurologists in diagnosis PNES but were more attuned to capture the subtleties of human behaviour, or subjective experiences as the effects of hidden internal conflicts, contributing a new lexicon in defining PNES.

The last aim was to investigate if two ad-hoc questionnaires investigating semiology and comorbidities of PNES coud be an alternative diagnostic tool when VEM is not available or not able to capture events. The two instrument assembled in this study, one for patient and one for their witnesses demonstrate to be useful tools, as they helped identifying variables predicting PNES diagnosis. Seven variables with high sensitivity (SE) and specificity (SP), of which 5 statistically significant, emerged as diagnostic predictors from patients questionnaire. They comprised three historical items: head injury, physical abuse and chronic fatigue; two warning signs: heart racing and tingling or numbness; one triggering sign: headache; one postictal symptom: physical pain. Side-to-side head movements and eyes closed were the statistically significant variables emerged from the analysis of witness questionnaire.

3.1 PREDICTING THE DIAGNOSIS OF PSYCHOGENIC NON EPILEPTIC SEIZURES (PNES) VERSUS EPILEPTIC SEIZURES (ES).

3.1.1 Introduction

The diagnosis of PNES constitutes a major challenge, because of greatly variable manifestations, often resembling those of epileptic seizures (ES) (Gedzelman and LaRoche, 2014). No single feature has proved to be pathognomonic, although a recent study found that the diagnosis is associated with a distinct cluster of signs (Syed et al 2011). As said before, the gold standard (GS) for a definitive diagnosis of PNES is the documentation of a normal EEG during events with semiology and a patient's history consistent with the diagnosis of PNES. Thus, the GS implies accessibility to a monitoring unit with specialized reviewers and services.

Nonetheless**,** VEM could fail to capture the events, despite induction attempts, and it will not differentiate certain types of frontal lobe ES from PNES. Moreover, the diagnosis of PNES, depends primarily on clinician's judgment and, unlike epilepsy, its reliability cannot be objectively verified by pathology or treatment outcome.

In an attempt to assess the accuracy of VEM, 22 board certified neurologists actively practicing in epilepsy centers from USA and Europe were asked to predict the diagnosis in 22 consecutive patients with mixed seizure types (PNES, ES and other nonepileptic events) based exclusively on VEM (Benbadis et al, 2009). Interrater agreement was moderate across all 3 diagnostic categories ($k = 0.57$) and was moderate for PNES ($k = 0.57$; substantial for ES ($k = 0.69$) and low for other nonepileptic episodes. The conclusion was that the diagnosis of these disorders based on combined VEM data presents inherent difficulties and particularly it might be affected by subjective components. Furthermore, adherence to current standard of care will prevent or delay the diagnosis in many patients worldwide who have no access to a VEM facility.

The ILAE task force considered advantages and limitations of home-recorded videos but did not recommend their use because the diagnostic yield of typical events recorded by witnesses has not been properly evaluated. Of the two modalities used in VEM, video recording is technically easier to obtain and less expensive than a video with simultaneous EEG. An earlier study demonstrated that, in a proportion of cases, neurologists could make a confident diagnosis of ES/PNES based entirely on videotapes recorded by hospital staff with a handheld camcorder (Samuel and Duncan, 1994). More recent studies have confirmed that the differential diagnosis between ES and PNES based on video alone is possible but requires neurological training (Ristić et al, 2015). Training of medical students through video-based modules of ES and PNES improves accuracy of seizure diagnosis (Seneviratne et al, 2014). It has been also demonstrated that trained epileptologists, blind to the EEG, contrary to untrained eyewitnesses, could easily

recognize key signs characteristic of either syndrome simply analyzing seizures on video, (Syed et al, 2011). Thus, there is evidence that in the hands of capable reviewers, video monitoring alone could represent a useful clinical tool.

The aim of this study was to investigate if, when and to what extent, a paroxysmal event captured on video and interpreted by experts in epilepsy could contribute to the differential diagnosis without the aid of simultaneous EEG. This information would be particularly relevant when the simultaneous EEG is not available or in case clinicians may elect to screen the events of patients with mixed seizure disorders on video before referral to a monitoring unit.

3.1.2 Methods

This study is part of a larger project currently in progress between the University of Rochester (UR) and three Italian Institutions: IRCCS Istituto di Ricerche Farmacologiche "Mario Negri", Milan; University of Messina, and Azienda Ospedaliera San Paolo, Milan, Italy. The study was approved by the Research Subject Review Board (RSRB) of the UR.

3.1.2.1 Patients

Patients 18 years and older consecutively admitted between July 1 and September 10, 2014 at the UR were asked to participate. Patients were excluded if they lacked intellectual capacity to answer questionnaires designed for the project. We enrolled prospectively all patients who consented. For each of them, at discharge, a representative audio-video segment, deprived of the EEG tracing, was submitted to five independent raters, for review and prediction of diagnosis. An epileptologist/electroencephalographer chose the most significant video of the seizures of each patient, among all the events recorded during VEM, that was used to reach the gold standard diagnosis in the Univeristy of Rochester Unit. Each video was clipped starting 20

minutes before and ending 20 minutes after the seizure event. Where possible, videos included testing of patient's responsiveness by staff.

3.1.2.2. Raters

The five raters were USA board certified neurologists/child neurologists (or the Italian equivalent) all practicing full time in tertiary Epilepsy Centers. The four raters from the Italian Institutions (R-1, R-2, R-3, R-4), were blind to the EEG findings, to the patient's history and comorbidities and were unaware of the final diagnosis. The fifth rater (R-5) was a faculty member of the epilepsy unit at UR. Though not responsible for direct patient care during the admission, R-5 was not blind but was specifically instructed not to access history, lab results or additional vignettes while reviewing the submitted video. This rater was included to investigate how awareness of ancillary clinical information would influence the rating.

Individual raters' profiles are reported in Table 3.1.1. All raters received their training through an epilepsy/clinical neurophysiology fellowship.

3.1.2.3. Procedure

Each rater was asked to review each video and render a diagnosis based only on audiovisual information. Raters were also asked if the video was technically satisfactory and "adequate", providing all the information necessary for the diagnosis and, if not, why. We considered a video adequate for the task if at least 3/5 raters agreed that the video was sufficiently informative.

Raters were given four diagnostic options and forced to choose one among the following: 1) ES, defined according to the 1981 ILAE classification (Commission 1981); 2) PNES, classified according to the six categories proposed by Seneviratne et al. (Seneviratne er al 2010): 1. Rhythmic motor; 2. Hypermotor; 3. Complex motor; 4. Dialeptic; 5. Nonepileptic auras; 6.

Mixed; 3) Other NES, due to paroxysmal non-epileptic events other than psychogenic (syncope or other dysautonomic manifestations, migraine, movement disorder, panic attacks, etc.); 4) "Cannot Say".

In addition, raters had to specify the main reasons leading to the diagnosis of choice and describe any behavioural observations contributing to their diagnostic decision.

Each rater worked independently and filed the data into a database set up at the IRCCS-Istituto di Ricerche Farmacologiche "Mario Negri" in Milano, Italy for statistical analysis.

Diagnostic accuracy was assessed as the ability of each rater to correctly predict the GS diagnosis, based on audiovisual evidence alone. The GS diagnosis was that established by the clinical team after a comprehensive evaluation of the patient's risk factors, co-morbidities, psychosocial status, results of neurological exam and neuro-imaging, video semiology, EEG findings including purely electrical seizures, and the results of monitoring other physiologic parameters (ECG, blood pressure, orthostatic testing, blood sugar, etc.) as appropriate. Accuracy in predicting the GS diagnosis was presented as the proportion of raters that correctly predicted the GS.

Inter-rater agreement was calculated among all raters, between pairs of raters, and between each rater and the GS using Fleiss' Kappa (Fleiss, 1971), with 95% confidence intervals (CI). Kappa values were used to assess overall agreement across all diagnostic categories (PNES, ES, Other NES, Cannot Say), and agreement in differentiating between the diagnosis of ES, PNES, Other NES and Cannot Say. Kappa values were classified as poor (<0.00), slight (0.01–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61– 0.80), almost perfect (0.81–1.00) (Landis and Koch, 1977). This classification of the magnitude of Kappa values is only for descriptive aims and does not refer to statistical significance. Data were analyzed using the SAS statistical package (version 9.2; SAS Institute Inc, Cary, NC, USA).

For each seizure that was reviewed, each rater's comments were surveyed and a list was compiled of all individual signs or symptoms identified as significant and their relative frequency. In addition, any specific observations (the sequence of certain manifestations, patient's affect, incongruous behaviour) was noted underpinning the raters' diagnostic reasoning.

3.1.3 Results

A total of 21 patients were enrolled. Each had at least one typical event recorded on video. Twenty patients reported one type of event. Case # 3 reported three types of events (3a, 3b, 3c.). Therefore, 23 videos were submitted to each rater for review.

3.1.3.1 Video quality

Raters considered "adequate" 10 of the 23 videos submitted (43%) whereas 13/23 (57%) were, in their judgement, "inadequate". This was mainly due to technical deficiencies or insufficient information (i.e., patient responsiveness not tested or incompletely tested, patient out of screen or poorly visible, defective audio).

3.1.3.2. Raters' accuracy in predicting the diagnosis

Table 3.1.2 shows the degree of concordance between raters' diagnostic predictions and GS diagnosis. The table includes the two cases (#7 and #16) where the clinical team had reached no definite diagnosis (NDD).

All five raters were correct in predicting the diagnosis in 7/23 cases (30.4%). Of these, three had ES and four PNES. In contrast, none of the five raters was in agreement with the GS diagnosis in 5/23 cases (21.7%): three had Other NES, one PNES and one NDD.

The ability to predict the diagnosis in the remaining 11 cases was intermediate (Table 3.1.2).

Since raters predicted the diagnosis based on the information contained in the video, each event was reviewed in order to try to identify the clues influencing the raters' decision. Success (5/5 raters correct) was related to events characterized predominantly by motor manifestations whereas failure (0/5 raters correct) was related to events characterized mainly by subjective sensory symptoms. Figure 3.1.1 shows the correlation between different degrees of accuracy and type of events recorded on video (motor in red, non-motor in blue). Success rate was higher for ES and PNES with motor manifestations and lower for Other NES, ES or PNES with no motor manifestations. Moreover, the number of signs identified as significant by the reviewer (shown in Table 3.1.3) seemed to correlate with accuracy. In the group of 7 videos correctly predicted by all raters the total number was 56, (average 8 signs/video, range: 5-11) compared to 20 in the group of 5 videos where all raters had failed (average 4 signs/video, range: 1-8).

Finally, to assess the influence of video quality on raters' accuracy, the rate of success was mapped against video quality as perceived by the reviewers. Out of the 7 cases where all raters were correct, 5 videos were adequate and 2 not adequate. In contrast, in the 5 cases where all raters had failed, the proportion was reversed with 1 video adequate against 4 not adequate.

3.1.3.3. Interrater agreement

The overall agreement among athe 5 raters was moderate (k= 0.52, 95% CI 0.44-0.60). The agreement was moderate for ES diagnosis (k=0.53, 95% CI 0.39-0.67), substantial for PNES (k=0.63, 95% CI 0.49 - 0.77), and fair for Other NES (k=0.21, 95% CI 0.07-0.35).

Table 3.1.4 shows inter-rater agreement within each pair of raters and between each rater and the GS. Combining all diagnoses, agreement between pairs of raters was higher between R-1 and R-2 (k=0.73), R-4 and R-5 (k=0.69), R-1 and R-5 (k=0.63). The pairs with the highest

agreement varied when limiting the diagnosis to PNES and ES (Other NES excluded). The overall agreement was in the moderate range for raters R-5 (k=0.58), R-4 (k=0.56), R-1 (k=0.49); it was substantial or above for two of the diagnostic categories: respectively, 0.81, 0.63, 0.82 for PNES; 0.90, 0.81, 0.81 (almost perfect) for ES. It was remarkably lower for Other NES. In comparison, kappa values for raters R-2 and R-3 were lower in all categories.

For all videos, agreement among the 5 raters was only slightly higher when inadequate videos were excluded (k=0.59, 95% CI 0.45-0.63).

3.1.3.4. Video content and raters' strategy leading to the diagnosis of choice.

Table 3.1.3 lists in order of decreasing frequency and by diagnostic category the specific terms used by raters to describe the signs that caught their attention. The observable signs and symptoms reported for the ES and PNES categories, where raters were most accurate in predicting the diagnosis, were by far more numerous than for the Other NES and Cannot Say categories.

The term "semiology" was the most frequently mentioned, either as positive statement, to indicate that it was a key element to the diagnosis, mostly in the case of ES and PNES, or as negative, to state that it was not consistent with either ES or PNES or was not sufficiently definable, that was most likely the case of Other NES.

3.1.4 Tables and Figure

Table 3.1.1. Individual profiles of raters

	R-1	**R-2**	**R-3**	**R-4**	**R-5**
Age (years)	56	48	39	39	32
Title	Neurologist, child neurologist	Neurologist	Child neurologist	Neurologist	Neurologist
Caring for patients with epilepsy (years)	30	15	9	9	2.5
Monthly hours for patients with epilepsy	50	60	30	150	100
Monthly visits for patients with seizures	25-50	>50	>50	>50	>50
Adults/children	90% adults	90% adults	100% children	99% adults	75% adults, 25% children
Blind to patients' info and EEG	Yes	Yes	Yes	Yes	No

Table 3.1.2. Accuracy of raters in predicting the diagnosis

Video	Adequacy of video	Semiology	Gold standard		Reviewer diagnosis					Accuracy
			Diagnosis	Seizure type	R-1	R-2	R-3	R-4	R-5	
1	Yes	Motor	ES	Focal with sec. gen.	ES	ES	PNES	ES	ES	4/5
2	No	Non-motor	Other NES	Dysautonomic	CANNOT SAY	CANNOT SAY	PNES	PNES	CANNOT SAY	0/5
3a	No	Motor	PNES	Complex motor	PNES	PNES	PNES	PNES	PNES	5/5
3b	No	Motor	PNES	Mixed	PNES	Es	PNES	PNES	PNES	4/5
3c	No	Non-motor	PNES	Non-epileptic aura	CANNOT SAY	ES	CANNOT SAY	CANNOT SAY	CANNOT SAY	0/5
4	Yes	Motor	PNES	Rhytmic motor	PNES	PNES	PNES	PNES	PNES	5/5
5	No	Motor	ES	Focal with sec. gen.	ES	ES	PNES	ES	ES	4/5
6	No	Motor	PNES	Rhytmic motor	PNES	PNES	PNES	PNES	OTHER	4/5
7	Yes	Non-motor	NDD	-	PNES	PNES	PNES	PNES	OTHER	0/5
8	Yes	Motor	ES	Focal with sec. gen.	ES	ES	ES	ES	ES	5/5
9	Yes	Motor	PNES	Rhytmic motor	PNES	PNES	PNES	CANNOT SAY	PNES	4/5

10	Yes	Motor	ES	Focal with sec. gen.	ES	ES	ES	ES	ES	5/5
11	Yes	Motor	ES	Focal with sec. gen.	ES	ES	ES	ES	ES	5/5
12	No	Non-motor	Other NES	Dysautonomic	CANNOT SAY	ES	CANNOT SAY	ES	CANNOT SAY	0/5
13	No	Motor	ES	Focal with sec. gen.	ES	ES	OTHER	CANNOT SAY	CANNOT SAY	2/5
14	Yes	Non-motor	ES	Simple Focal	CANNOT SAY	CANNOT SAY	CANNOT SAY	ES	ES	2/5
15	Yes	Motor	ES	Complex Focal	ES	PNES	PNES	ES	ES	3/5
16	No	Non-motor	NDD	-	ES	ES	CANNOT SAY	CANNOT SAY	CANNOT SAY	3/5
17	No	Non-motor	PNES	Non-epileptic aura	PNES	PNES	CANNOT SAY	PNES	PNES	4/5
18	No	Non-motor	Other NES	Dysautonomic	CANNOT SAY	CANNOT SAY	OTHER	OTHER	OTHER	3/5
19	Yes	Motor	PNES	Complex motor	PNES	PNES	PNES	PNES	PNES	5/5
20	No	Non-motor	Other NES	Dysautonomic	CANNOT SAY	CANNOT SAY	CANNOT SAY	CANNOT SAY	CANNOT SAY	0/5
21	No	Non-motor	PNES	Dialeptic	PNES	PNES	PNES	PNES	PNES	5/5

Legend: ES= epileptic seizures; PNES= psychogenic non-epileptic seizures; NES= non-epileptic seizures.

Table 3.1.3. Signs and symptoms leading to the diagnosis

Signs	Compound frequency	ES	PNES	Other NES	CANNOT SAY
Semiology	28	1, 5, 10, 11, 14, 15	3a, 3b, 4, 6, 17, 19, 21	2, 18, 20	7
Wax/waning	21	1, 15	3a,3b, 4, 6, 9, 17, 19, 21		7
Subjective feelings	17		3c, 4, 17	12, 18, 20	
Automatisms	13	5, 8, 10, 13, 15			
Shaking	11	1, 15	3a, 4, 6, 9,		7
Long duration	10		3a, 3b, 4, 9, 17, 19	2	
Dystonic posturing	10	1, 5, 8, 10, 15	3b, 4, 19, 21		
Slow Post-ictal recovery	10	5, 8, 10, 11, 14	3b		
Short duration	9	5, 10, 11, 15	3c	18	
Eyes close	8		3a, 4, 19, 21		
[Forced] head deviation	8	1, 5, 10, 11, 15			
Expression of emotionality	7		4, 17		
Modality of onset: out of sleep	7	1, 8, 13		2	
Eyes open	6	5, 8, 10			
Increased tone	6	1, 5, 10, 11	9		
Crying	6		21		7
Loss of consciousness	6	5, 10, 11, 15	3b, 3c		
Preserved consciounsess	6		3a, 3b,	2	7, 16
Tremors	5		3a, 3b, 6		7
Slumping	5		3a, 19, 21		
Modality of onset: abrupt	5	5, 10	4, 9, 21		
Modality of onset: gradual	5	15	3a, 3b, 9		
Confusion	4	8, 10, 14			
Fast Post-ictal recovery	4		3a, 3c, 4		
Asynchrony	3	1,5,10			

Tingling	2		3c, 21	
Arrhythmicity	1		19	
Internal sensation	1			7
Visual distortion	1			16
Hyperventilation	1			7
Synchrony	0	0		
Rhythmicity	0	0		

Legend: ES= epileptic seizures; PNES= psychogenic non-epileptic seizures; CANNOT SAY= no diagnosis possible.
Numbers in the table refer to the specific seizure-video for which that particular sign was mentioned as being significant.

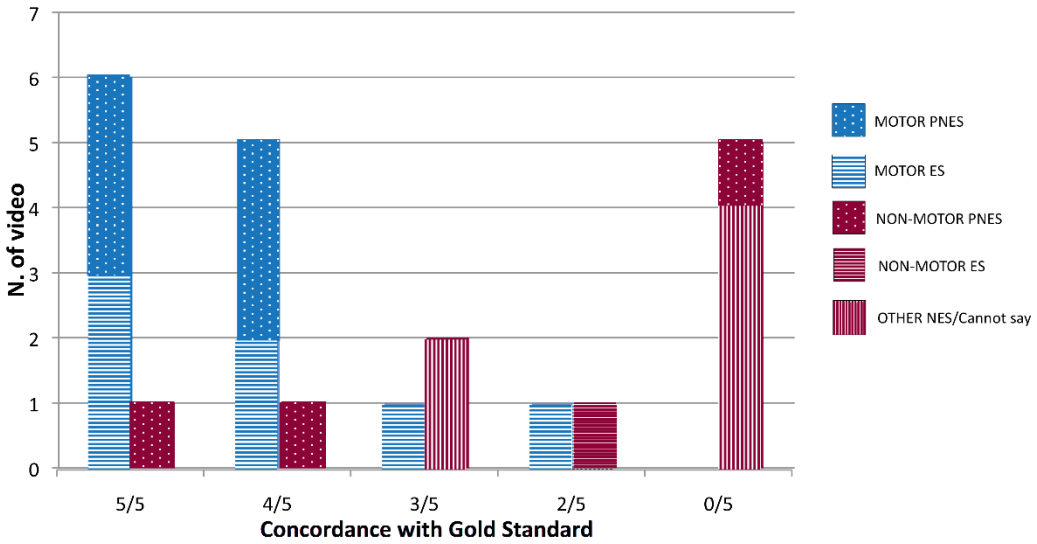
Table 3.1.4. Interrater agreement

	Overall		PNES		ES		Other NES	
Pair	**Kappa**	**95% CI**	**Kappa**	**95% CI**	**Kappa**	**95% CI**	**Kappa**	**95% CI**
R-5 vs. R-1	0.63	0.38 - 0.88	0.81	0.40 - 1.00	0.70	0.29 - 1.00	-0.07	-0.48 - 0.34
R-5 vs. R-2	0.37	0.12 - 0.62	0.62	0.21 - 1.00	0.35	-0.06 - 0.76	-0.07	-0.48 - 0.34
R-5 vs. R-3	0.44	0.19 - 0.69	0.37	-0.04 - 0.78	0.49	0.08 - 0.90	0.33	-0.08 - 0.74
R-5 vs. R-4	0.69	0.44 - 0.94	0.62	0.21 -1.00	0.90	0.49 - 1.00	0.45	0.04 - 0.86
R-1 vs. R-2	0.73	0.44 - 1.00	0.82	0.41 - 1.00	0.63	0.22 - 1.00	-*	-
R-1 vs. R-3	0.48	0.21 - 0.75	0.56	0.15 - 0.97	0.40	-0.01 - 0.81	-0.05	-0.46 - 0.36
R-1 vs. R-4	0.54	0.27 - 0.81	0.82	0.41 - 1.00	0.62	0.21 - 1.00	-0.02	-0.43 - 0.39
R-2 vs. R-3	0.34	0.07 - 0.61	0.56	0.15 - 0.97	0.25	-0.16 - 0.66	-0.05	-0.46 - 0.36
R-2 vs. R-4	0.40	0.11 - 0.69	0.63	0.22 - 1.00	0.45	0.04 - 0.86	-0.02	-0.43 - 0.39
R-3 vs. R-4	0.48	0.23 - 0.73	0.56	0.15 - 0.97	0.40	-0.01 - 0.81	0.64	0.23 - 1.00

R-5 vs. GS	0.58	0.33 - 0.83	0.81	0.40 - 1.00	0.90	0.49 - 1.00	0.15	-0.26 - 0.56
R-1 vs. GS	0.49	0.24 - 0.74	0.82	0.41 - 1.00	0.81	0.40 - 1.00	-0.10	-0.51 - 0.31
R-2 vs. GS	0.35	0.08 - 0.62	0.63	0.22 - 1.00	0.45	0.04 - 0.86	-0.10	-0.51 - 0.31
R-3 vs. GS	0.30	0.05 - 0.55	0.39	-0.02 - 0.80	0.40	-0.01 - 0.81	0.23	-0.18 - 0.64
R-4 vs. GS	0.56	0.31 - 0.81	0.63	0.22 - 1.00	0.81	0.40 - 1.00	0.32	-0.09 - 0.73

*No reviewers give the response “Other”. Legend: PNES= psychogenic non-epileptic seizures; ES= epileptic seizures.

Figure 3.1.1. Correlation between accuracy and type of events



Legend: Figure 1 shows the association between degrees of accuracy (x axis) and type of events recorded on video (number of videos on y axis): motor PNES in blue with dots, motor ES in blue with orizontal lines, non-motor PNES in red with dots, non-motor ES in red with orizontal lines and other NES/cannot say in red with vertical lines.

ES= epileptic seizures; PNES= psychogenic non-epileptic seizures; NES= non-epileptic seizures.

3.2 Engaging Psychiatrists in the diagnosis of PNES. What can they contribute?

3.2.1 Introduction

The second step of the MI-RO Study was to investigate if, how, and to what extent a group of psychiatrists could predict the diagnosis on pure visual information, reviewing blindly the same videos submitted to epileptologists in the previous part of the study, and to compare the accuracy as well as the criteria leading to the diagnosis of the psychiatrists against the epileptologists.

Based on the results of previous trials challenging various categories of medical providers in comparison to fully trained epileptologists (Syed et al, 2011; Samuel et al, 1994; Ristić et al 2015; Seneviratne et al, 2014; MacDonald et al, 2014), our expectation was that psychiatrists would fail, mainly because largely unfamiliar with the semiology of ES and because the characteristic features that distinguish ES from PNES reflect neurological measures predominantly reported by epileptologists.

3.2.2 Methods

The study population is the same reported in the previous step of the MI-RO Study (Erba et al, 2016).

3.2.2.1 Raters and Procedure

Unlike the previous study, the four raters were board certified psychiatrists, with varying degree of seniority, of knowledge about epilepsy and exposure to patients with seizure disorders (Table 3.2.1). Each rater was blind to the EEG findings, to the patient's history and comorbidities, and unaware of the final diagnosis established by the clinical team. The task was to review the same videos submitted to epileptologists in the previous study [8] and render a diagnosis out of the following options:

- ES, defined according to the 2017 ILAE classification (Fisher et al, 2017);

- PNES, classified according to the six categories proposed by Seneviratne et al (2010): 1. Rhythmic motor, 2. Hypermotor, 3. Complex motor, 4. Dialeptic, 5. Nonepileptic auras, and 6. Mixed;
- Other nonepileptic seizures (NES), due to paroxysmal nonepileptic events other than psychogenic (syncope or other dysautonomic manifestations, migraine, movement disorder, panic attacks, etc.);
- "Cannot Say."

In addition, raters had to specify the reasons leading to the diagnosis and describe any behavioural observations contributing to their diagnostic decision.

Each rater worked independently and filed the data into a database set up at the IRCCS-Pharmacological Research Institute "Mario Negri" in Milano, Italy, for statistical analysis. Diagnostic accuracy was assessed as the ability of each individual rater to correctly predict the GS diagnosis, based on audiovisual evidence alone. The GS diagnosis was the result of a comprehensive evaluation of multiple factors. These included the patient's risk factors, comorbidities and psychosocial status; neurological, neuroimaging, interictal EEG findings and the characterization of the events (when recorded). This was based on video semiology, ictal EEG findings (including purely electrical seizures), and the results of monitoring other physiologic parameters such as electrocardiography, blood pressure, orthostatic testing, blood sugar, and so on as appropriate. In the two cases where by GS no diagnosis was possible (NDP), the rater's response "Cannot say" was considered correct. Raters' accuracy in predicting the GS diagnosis was presented as the proportion of raters that correctly predicted the GS.

3.2.2.2 Statistical analysis

As with the diagnosis made by the epileptologists, interrater agreement was calculated among all raters, between pairs of raters, and between each rater and the GS using Fleiss' Kappa (Fleiss, 1971) with 95% confidence intervals (CIs).

3.2.3 Results

Table 3.2.2 correlates the clinical characteristics of the 23 events submitted for review with the accuracy of the four blind psychiatrists vs. four blind epileptologists in predicting the GS diagnosis as a group and as individual raters.

All four psychiatrists were concordant and correct (4/4) in 3/23 video-events, compared to 8/23 when raters were trained epileptologists. The superiority of the epileptologists is also apparent when the concordance in accurately predicting the diagnosis for each individual video was < 4/4 (i.e.: 3/4; 2/4; 1/4; 0/4). Comparison between the two groups shows 12 points (+) advantage in favor of the epileptologists compared to 4 points in favor of the psychiatrists.

Kappa values confirm the discrepancy between the two groups. While overall concordance among the four epileptologists was 0.50, it was 0.18 among the four psychiatrists, similar differences are found in the Kappa values by type of seizures, varying from 0.20 to 0.66 (epileptologists) and from -0.03 to 0.21 (psychiatrists) (Table 3.2.3). Likewise, agreement within pairs of epileptologists showed Kappa values varying from 0.34 to 0.73 (Table 3.2.4) whereas agreement among pairs of psychiatrists was much lower, ranging from –0.2 to 0.37 (Table 3.2.5). Surprisingly, however, agreement of each individual rater with the GS yielded superimposable K values in the two groups, ranging from 0.30 to 0.56 among epileptologists (Table 3.2.4) and from 0.01 to 0.45 among psychiatrists (Table 3.2.5). Therefore, despite widespread disagreement among themselves and frequent failures as a group, our results indicate that individual psychiatrists were almost as accurate as epileptologists in predicting the correct diagnosis after reviewing the same events recorded on video.

Success or failure was not correlated to any particular type of event (epilepsy, psychogenic, other physiologic or cannot say). However, raters PS3 and PS4 chose the diagnosis “Cannot say” more often (7/23) than PS1 and PS2 (3/23) while the epileptologists were less variable (6/23, R1 and R3; 4/23, R-2; 5/23, R-4).

The comments provided by the four psychiatrists to justify the diagnosis of choice varied considerably in format and detail from rater to rater, with PS1 being the most attentive and articulate. In essence, like the epileptologists, psychiatrists paid considerable attention to body movements, ostensibly the most obvious signs of the events' semiology exhibited on video. Starting from the body parts involved, they considered head/eyes/mouth deviation and lateralized limb posturing as clear indicators of ES versus predominant involvement of trunk/hips/fingers as suggestive of PNES. Similarly, they remarked on resistance to eye opening, 'one single shake', sudden onset or abrupt interruption, 'on/off' and high frequency movements as indicators of PNES, but also emphasised more subtle behavioural aspects such as 'slow motion', irregular, unpredictable, shaking. Likewise, they often failed to see the progression of movements from tonic to clonic, from fast to slow, from focal to generalized to the more disorganized motions defined as other "non-epileptic" or pseudo-myoclonic. Finally, while directly mentioning specific types of movement as 'side-to-side' or 'out of synchrony', they preferred describing pelvic thrusting as 'arc de circle' or 'hips more involved' or 'body motions with sexual connotations'.

Special attention was given to the presence of "automatisms", distinguishing stereotyped, out of context, complex motor activity (such as aimlessly looking around), typical of complex focal seizures, from comparable motor manifestations that, at close scrutiny, appeared more purposeful or deliberate such as 'subject puts herself at the center of attention' (17) or 'slow movements of one hand only' (3b) or both hands (21) and more "in context" such as 'movements of postural adjustment' or 'mirror movements' imitating the examiner (3a) or 'partially in touch with the context but distant, as if confused or waiting to gain time' (14). Likewise, certain gestures such as 'bringing hands to the chest' or to the head 'as if in pain' or 'holding arms by the breasts' (3b, 4) were interpreted by psychiatrists as indicative of an inner conflict or suffering. With few exceptions, most of these observations were mentioned to support the diagnosis of PNES.

Finally, psychiatrists pointed out a number of motor system's inconsistencies such as 'holding up a seemingly hypotonic arm', 'falling without body hypotonia' or discrepancies such as the incompatible association between level of consciousness and myoclonic movements' (3b), as well as behavioural inconsistencies such as the subject's calm, 'almost placid' appearance during motor arrest 'while holding hand with the nearest person' (21). Table 3.2.6 shows a series of representative comments typically made by psychiatrists correlating each observation with the number of videos, the rater, the rater's diagnosis and the GS diagnosis.

3.2.4 Tables

Table 3.2.1. Individual profile of raters.

Rater	Years in practice	Formal education in epilepsy (Yes/No)	N. of patients with seizure disorders seen during clinical practice	Degree	Specialty training
PS1	30	YES	Hundreds	MD	Psychiatry
PS2	12	YES	6/year	MD	Psychiatry
PS3	30	NO	15/year	MD	Psychiatry
PS4	10	NO	15/year	MD	Psychiatry

Table 3.2.2. Accuracy of psychiatrists vs. epileptologists in predicting the gold standard diagnosis

Video	Semiology	Gold standard	PS1	PS2	PS3	PS4	Psychiatrists'accuracy	Epileptogists' accuracy
1	Motor	ES	ES	PNES	ES	ES	3/4	3/4
2	Non-motor	Other	ES	Cannot say	PNES	ES	0/4	0/4
3a	Motor	PNES	PNES	PNES	PNES	PNES	4/4	4/4
3b	Motor	PNES	PNES	PNES	ES	PNES	3/4	3/4
3c	Non-motor	PNES	PNES	Cannot say	Cannot say	Other	1/4 +	0/4
4	Motor	PNES	PNES	PNES	PNES	Cannot say	3/4	4/4 +
5	Motor	ES	ES	ES	ES	PNES	3/4	3/4
6	Motor	PNES	Cannot say	PNES	Other	Cannot say	1/4	4/4 + + +
7	Non-motor	NDP	PNES	Other	Cannot say	PNES	1/4 +	0/4
8	Motor	ES	ES	PNES	ES	ES	3/4	4/4 +
9	Motor	PNES	ES	PNES	PNES	ES	2/4	3/4 +
10	Motor	ES	ES	ES	ES	PNES	3/4	4/4 +
11	Motor	ES	ES	ES	ES	ES	4/4	4/4
12	Non-motor	Other	Cannot say	ES	Cannot say	Cannot say	0/4	0/4
13	Motor	ES	ES	ES	ES	Cannot say	3/4 +	2/4
14	Non-motor	ES	Other	ES	Cannot say	Cannot say	1/4	1/4
15	Motor	ES	ES	ES	ES	PNES	3/4 +	2/4
16	Non-motor	NDP	Other	ES	Cannot say	PNES	1/4	2/4 +
17	Non-motor	PNES	Other	Cannot say	Cannot say	PNES	1/4	3/4 + +
18	Non-motor	Other	Other	Other	Cannot say	Cannot say	2/4	2/4
19	Motor	PNES	Other	PNES	PNES	ES	2/4	4/4 + +
20	Non-motor	Other	Cannot say	ES	ES	Cannot say	0/4	0/4
21	Non-motor	PNES	PNES	PNES	PNES	PNES	4/4	4/4
							4+	12+

PS: psychiatrist; NDP: no diagnosis possible; ES: epileptic seizure; PNES: psychogenic non-epileptic seizure.

Table 3.2.3. Agreement among four psychiatrists and among four epileptologists

	Kappa	95% CI	
Psychiatrists			
Overall	0,18	0,08	0,28
PNES	0,21	0,03	0,39
ES	0,29	0,11	0,47
Other	-0,03	-0,21	0,15
Epileptologists			
Overall	0.50	0,32	0,68
PNES	0.66	0,54	0,78
ES	0.48	0,36	0,60
Other	0.20	0,08	0,32

ES: epileptic seizure; PNES: psychogenic non-epileptic seizure

Table 3.2.4. Agreement within pairs of epileptologists and between each epileptologist and gold standard

	Overall		PNES		ES		Other	
Pair	**Kappa**	**95% CI**	**Kappa**	**95% CI**	**Kappa**	**95% CI**	**Kappa**	**95% CI**
R1 vs. R2	0.73	0.44 - 1.00	0.82	0.41 - 1.00	0.63	0.22 - 1.00	-*	-
R1 vs. R3	0.48	0.21 - 0.75	0.56	0.15 - 0.97	0.40	-0.01 - 0.81	-0.05	-0.46 - 0.36
R1 vs. R4	0.54	0.27 - 0.81	0.82	0.41 - 1.00	0.62	0.21 - 1.00	-0.02	-0.43 - 0.39
R2 vs. R3	0.34	0.07 - 0.61	0.56	0.15 - 0.97	0.25	-0.16 - 0.66	-0.05	-0.46 - 0.36
R2 vs. R4	0.40	0.11 - 0.69	0.63	0.22 - 1.00	0.45	0.04 - 0.86	-0.02	-0.43 - 0.39
R3 vs. R4	0.48	0.23 - 0.73	0.56	0.15 - 0.97	0.40	-0.01 - 0.81	0.64	0.23 - 1.00
R1 vs. GS	0.49	0.24 - 0.74	0.82	0.41 - 1.00	0.81	0.40 - 1.00	-0.10	-0.51 - 0.31
R2 vs. GS	0.35	0.08 - 0.62	0.63	0.22 - 1.00	0.45	0.04 - 0.86	-0.10	-0.51 - 0.31
R3 vs. GS	0.30	0.05 - 0.55	0.39	-0.02 - 0.80	0.40	-0.01 - 0.81	0.23	-0.18 - 0.64
R4 vs. GS	0.56	0.31 - 0.81	0.63	0.22 - 1.00	0.81	0.40 - 1.00	0.32	-0.09 - 0.73

*no reviewers give the response “Other”.
ES: epileptic seizure; PNES: psychogenic non-epileptic seizure: R: rater; GS: gold standard; CI: confidence interval

Table 3.2.5. Agreement within pairs of psychiatrists and between each psychiatrist and gold standard

	Overall		PNES		ES		Other	
Pair	**Kappa**	**95% CI**	**Kappa**	**95% CI**	**Kappa**	**95% CI**	**Kappa**	**95% CI**
PS1 vs PS2	0,19	-0.06; 0.44	0,31	-0.10; 0.72	0,27	-0.14; 0.68	0,16	-0.25; 0.57
PS1 vs PS3	0,27	0.02; 0.52	0,32	-0.09; 0.73	0,63	0.22; 1.00	-0,15	-0.56; 0.26
PS1 vs PS4	0,34	0.09; 0.59	0,31	-0.10; 0.72	0,51	0.10; 0.92	-0,15	-0.56; 0.26
PS2 vs PS3	0,37	0.12; 0.62	0,51	0.10; 0.92	0,45	0.04; 0.86	-0,07	-0.48; 0.34
PS2 vs PS4	-0,2	-0.45; 0.05	-0,09	-0.50; 0.32	-0,29	-0.70; 0.12	-0,07	-0.48; 0.35
PS3 vs PS4	0,06	-0.21; 0.33	-0,09	-0.50; 0.32	0,11	-0.30; 0.52	-0,05	-0.46; 0.36
PS1 vs GS	0,39	0.14; 0.64	0,51	0.10; 0.92	0,72	0.31; 1.00	0,03	-0.38; 0.44
PS2 vs GS	0,43	0.18; 0.68	0,63	0.22; 1.00	0,53	0.12; 0.94	0,23	-0.18; 0.64
PS3 vs GS	0,45	0.20; 0.70	0,51	0.10; 0.92	0,72	0.31; 1.00	-0,12	-0.53; 0.29
PS4 vs GS	0,01	-0.24; 0.26	0,09	-0.32; 0.50	0,18	-0.23; 0.59	-0,12	-0.53; 0.29

ES: epileptic seizure; PNES: psychogenic non-epileptic seizure; PS: psychiatrist; GS: gold standard; CI: confidence interval

Table 3.2.6. Original observations of psychiatrists

Video #	Original observations	Diagnosis of choice	Diagnosis GS
3a	Apparent loss of contact after *prolonged* photic stimulation (PS1)	PNES	PNES-Motor
	Purposeful postural adjustments during eyes opening and closing (PS1)	PNES	PNES-Motor
	Absence of agitated behaviour + calm breathing (PS3)	PNES	PNES-Motor
	Event induced by stress (prolonged photic stimulation) (PS4)	PNES	PNES-Motor
3b	Subtly regains contact bringing hands to chest (PS1)	PNES	PNES-Motor
	Apparent thoracic pain + slow hand movements (PS4)	PNES	PNES-Motor
3c	Bilateral sensory misperceptions (PS1)	PNES	PNES-Non motor
	Mantains contact during psychomotor slowing (PS1)	PNES	PNES-Non motor
	Tendency to disengage from context (PS1)	PNES	PNES-Non motor
4	No pelvic trusting but movements with sexual connotation (PS1)	PNES	PNES-Motor
	Apparent confusion during perception of pain (PS1)	PNES	PNES-Motor
	"Non-epileptic" movements of arms and legs (PS3)	PNES	PNES-Motor
	Indifferent to what has happened (PS3)	PNES	PNES-Motor
	Alert behaviour during seizure (PS4)	PNES	PNES-Motor
7	Looks astonished, slow motions and diffuse malaise (PS1)	PNES	NDP-Non motor
	"Dissociation symptoms" (feels like shaking even if not apparent) (PS2)	Other	NDP-Non motor
	Emotional behaviour (PS2)	Other	NDP-Non motor
8	Twilight state, with partial detachment (PS1)	EPILEPSY	EPILEPSY-Motor
9	Arc de circle (PS2)	PNES	PNES-Motor

	Questionable impairment of consciousness/seizure only in presence of witness (PS3)	PNES	PNES-Motor
10	Indifference (PS4)	PNES	EPILEPSY-Motor
13	"Morpheic" event (PS2)	EPILEPSY	EPILEPSY-Motor
14	Appears partially in touch with context but distant, as if confused or wanting to gain time (PS1)	Other	EPILEPSY-Non motor
15	Indifferent attitude (PS4)	PNES	EPILEPSY- Motor
17	During the event, subject puts herself at the centre of attention (PS1)	Other	PNES-Non motor
19	Seizure only when people present (PS3)	PNES	PNES-Motor
21	Falls on bed (no injury) without apparent reasons (PS1, PS2, PS3)	PNES	PNES-Non motor
	"Almost placid" during motor arrest + holding hand of nearest person if still in touch (PS1)	PNES	PNES-Non motor

PNES: psychogenic non-epileptic seizure; GS: gold standard; PS: psychiatrist; NDP: no diagnosis possible.

3.3 A new patient-oriented questionnaire for differentiating epileptic from psychogenic non-epileptic seizures. Value, limitations, future directions

3.3.1 Introduction

In the previous sections of this study we investigated how experienced epileptologists, blind to the EEG findings and other clinical information, can predict the diagnosis by simply reviewing the semiology of events captured on video in about one third of cases (Erba et al., 2016). Here we investigate the predictive value of structured questionnaires designed to collect directly from patients and eyewitnesses information about personal history, characteristics of the events and specific risk factors.

The aim was to establish whether and to what extent such instrument could represent a useful addition to the investigation routinely performed by care providers in specialized centers or be a viable surrogate when such facilities are not accessible.

3.3.2 Methods

3.3.2.1 Eligibility Criteria and Setting

Consecutive new patients above the age of 18 and with no evidence of cognitive impairment admitted for investigation of seizures to the long term monitoring unit of the University of Rochester, NY, were eligible for the study.

3.3.2.2 The questionnaires

Two ad hoc questionnaires, one for patients (Questionnaire A) and one for witnesses (Questionnaire B), were assembled based on features reported in the literature as characteristically associated with ES or PNES and all other signs and symptoms that, according to our clinical experience, could help differentiating the two syndromes. They consisted of an eclectic array of signs and symptoms known from the literature to correlate with the diagnosis of either ES or PNES. They incorporated items that were part of pre-existing instruments, one in particular that, based on sensitivity/specificity values, had identified 3 diagnostic indicators for PNES and 3 for ES out of 45 video-documented signs

(Syed et al 2011). However, since our aim was to build a comprehensive, broad-based instrument, we equally considered analogous tools used for other more specific purposes (Rugg-Gunn et al 2001) as well as reports highlighting the discriminatory value of single clinical features (Rosemergy et al, 2013; Sen et al 2007). In addition, we added all other signs and symptoms that, according to our clinical experience, could help differentiating the two disorders. Contrary to previous questionnaires, mostly designed to guide trained professionals through an exhaustive scrutiny of the semiology of the events (Syed et al 2011; Rugg-Gunn et al 2001), the distinctive features of Questionnaire A and B were to encourage patients and eyewitnesses to tell their story, how they felt, what they saw. Consequently, the wording had to be easily accessible to lay/untrained people and was geared to explore subjective experiences (patients) and the recall of critical observations (eyewitnesses). Questionnaire A, focused on patients past history, specific risk factors, precipitating events and comorbidities. It also gave special attention to triggering or warning signs and to the subjective experiences that may occur in patients with either ES or PNES before, during and after the typical events. Questionnaire B focused on the semiology of the events, namely the manifestations reportedly characteristic of ES and PNES, to document the objective observations made by the eyewitness when the patient is or appears to be unconscious.

It is well documented that the discriminatory abilities of caregivers in detecting characteristic features of the events is far inferior to that of epileptologists (Syed et al 2011; Rugg-Gunn et al 2001). In addition, retrospective contributions of eyewitness depend on the recall of what an untrained observer has noticed at the time of the event. Thus, the aim of Questionnaire B was twofold: 1) determine how contributory an account based on the late recollections of a nonprofessional witness can be; 2) define which signs, among those reported as typically associated with ES or PNES, are more likely to be noticed and reported. When patients and witnesses described more than one type of event (i.e. convulsions, staring, unresponsiveness, loss of time, etc.), the same set of questions was replicated for each of the

three most frequent events. Efforts were made to formulate the questions in lay terms at 7th grade level to optimize comprehension and facilitate self-administration. A non-physician assistant was present during the collection of data to clarify issues when necessary. Questionnaires A and B were administered prospectively, during the early part of the admission before the diagnosis was known.

Questionnaire A was revised after testing the first set of 21 subjects, mainly to improve clarity without altering the content. During this process, and without the benefit of an interim analysis, it appeared that some questions pertaining to symptoms of somatization were too generic for an effective discrimination between ES and PNES. Therefore, they were removed. Nonetheless, in the final analysis patients' answers to all questions, including those removed, were assessed.

The full sets of questions contained in the original version of Questionnaire A and Questionnaire B are available in the Appendix.

The electronic version of questionnaires was based on REDCap and the patients were instructed to use by themselves the program. REDCap is a web application for building and managing online surveys and databases. There was always a study-staff person present ready to help where needed.

3.3.2.3 Final diagnosis

The final diagnosis was based on the convergence of the following: presence, or absence, of specific risk factors in the patient's history; findings on VEM/EKG monitoring; results of psychiatric and neurological assessments. In case a definite diagnosis could not be reached the case was removed from analysis.

3.3.2.4 Data analysis

Using the information obtained from each single question included in questionnaires A and B, a list of variables representing specific signs, symptoms and risk factors was created. Each variable was coded as present, absent or "missing" when the patient/witness did not know

or did not want to respond. If the patient had more than one seizure type, a sign, symptom or risk factor was considered as present if recorded in one or more seizure types and as absent if recorded in none. Since the aim was to assess the discriminating value, we independently calculated specificity (SP) and sensitivity (SE) of each variable analyzing the direct responses of patients and witnesses against the final diagnosis. We compare exclusively patients with proven diagnosis of PNES versus patients with proven ES. All subjects with both PNES and ES or with other types of events were excluded. In order to identify variables that would correctly confirm or exclude a PNES diagnosis with high probability and to exclude those too common or too uncommon in either group, we followed the criteria adopted by Syed et al. (Syed et al., 2011): 1) either SE or SP must be at least 80%; 2) both SE and SP must be no less than 50%. In addition we tabulated all variables with SE and SP between 60% and 80%. We also tested the statistical significance of the selected variables using the Fisher's exact test.

3.3.3 Results

3.3.3.1 Study sample

A total of 50 patients were enrolled in the study. The final diagnosis was PNES (20), ES (12), Other type (5), ES+PNES (1) and no diagnosis possible (12). Four subjects were unable to complete questionnaire A because of early discharge. From the remaining 46 subjects, 18 were excluded due to diagnosis of other events or no diagnosis, leaving 28 questionnaires A eligible for analysis: 17 were completed by patients with PNES (76% female; mean age 39.2 / standard deviation, SD 12.5) and 11 by patients with ES (64 % female; mean age 40.4 / SD 19.4).

Questionnaire B was not obtained in 21 cases because a reliable witness could not be reached or identified. Of the remaining 29 subjects, 13 were excluded because the diagnosis was other events (5) or no diagnosis (8). This left a total of 16 questionnaires B eligible for

analysis: 6 pertained to patients with PNES (gender 50% female; mean age 34.0 / SD 9.5) and 10 to patients with ES (gender 70% female; mean age 41.6 / SD 20.0).

3.3.3.2 Patient burden

The task of filling the questionnaire was well tolerated. Approximately half of the participants chose to self-administer the questionnaire and had no difficulties in using the electronic version. Most subjects required little or no assistance from the clinical coordinator who was present during the task.

3.3.3.3 Questionnaire acceptability

In this study, with the exception of one patient who refused to discuss his upbringing, all other subjects had no apparent hesitation in disclosing history of abuse or other sensitive information despite being aware that they were entitled to skip embarrassing questions.

3.3.3.4 Sensitivity (SE) and Specificity (SP) of patient's responses to questionnaire A

Table 3.3.1 shows the 7 variables in Questionnaire A (patient) that met the pre-set criteria of high SE and SP, indicating whether the variable was present or absent in either group. Three variables pertained to the event's prodromal phase: headache, heart racing and tingling or numbness; one to the post-ictal phase: physical pain. The remaining three concerned the subject's history: two risk factors (head injury, physical abuse) and chronic fatigue. Sexual and emotional abuse and none of the psychiatric co-morbidities reached the discriminating threshold as they were seldom reported in both groups. The p-value was significant for all variables except for tingling and numbness ($p= 0.1150$) and physical abuse ($p= 0.0540$). Response rate was complete for all questions except for chronic fatigue, an item investigated only in the early version of questionnaire A.

Table 3.3.2 shows the 6 variables in questionnaire A below the pre-set threshold but with SE/SP no less than 50% and either SE or SP between 60% and 80%. Again, three of them

concerned the prodromal and post-ictal phase and three the patient's history, one of which was a risk factor (emotional abuse).

3.3.3.5 Sensitivity and Specificity of the witness responses to questionnaire B

Table 3.3.3 shows the only 2 variables in Questionnaire B that reached the discriminating threshold and significant p-value. They represented two ictal signs: head moving from side to side and eye closure, observed in at least one of the witnessed seizures.

Table 3.3.4 shows the 4 variables in Questionnaire B below threshold but with SE/SP no less than 50% and SE or SP between 60% and 80%. Three were related to the event's semiology (i.e. ictal on/off movements) and one to a special ictal function (being talked out of seizures.)

All other variables of Questionnaire A and B did not reach the minimum threshold (see Supplementary Tables 3.3.1 and 3.3.2).

3.3.4 Tables

Table 3.3.1. Patient questionnaire: PNES (#17) vs. ES (#11): list of all variables with sensitivity or specificity above pre-set threshold.

Question	Variable	PNES			ES			SE	SP	p-value
		Present	Absent	Not indicated	Present	Absent	Not indicated			
13	Headache (trigger)	11	6	-	1	10	-	64.7	90.0	0.0060
24/33/42	Heart racing (Warning)	9	8	-	1	10	-	52.9	90.9	0.0407
24/33/42	Tingling or numbness (Warning)	9	8	-	2	9	-	52.9	81.8	0.1150
30/39/48	Feel in physical pain (after seizure)	10	7	-	1	10	-	58.8	90.9	0.0161
50	Head injury with loss of consciousness ≥5 min. (History)	10	7	-	1	10	-	58.8	90.9	0.0161
56	Physical abuse (History)	10	7	-	2	9	-	58.8	81.8	0.0540
62	Fatigue* (History)	6	0	11	1	6	4	100	85.7	0.0047

Legend: PNES psychogenic non-epileptic seizures; ES epileptic seizures; SE sensitivity; SP specificity.

*Investigated only in the first 21 patients.

Table 3.3.2. Patient questionnaire: PNES (#17) vs. ES (#11): list of all variables with both sensitivity and specificity no less than 50% and sensitivity or specificity between 60 and 80 (below the pre-set threshold).

Question	Variable	PNES			ES			SE	SP	p-value
		Present	Absent	Not indicated	Present	Absent	Not indicated			
15	Bright/flashing lights (trigger)	9	8	.	4	7	.	52.94	63.64	0.4601
16	Feeling overwhelmed (trigger)	12	5	.	4	7	.	70.59	63.64	0.1212
28/37/46	Trouble speaking (after seizure)	11	6	.	4	7	.	64.71	63.64	0.2458
58	Emotional abuse (History)	9	8	.	4	7	.	52.94	63.64	0.4601
67	Gerd reflux (Diagnosis)	3	3	11	1	6	4	50.00	85.71	0.2657
90	Self-inflicted injuries (History)	9	8	.	3	8	.	52.94	72.73	0.2530

Legend: PNES psychogenic non-epileptic seizures; ES epileptic seizures; SE sensitivity; SP specificity.

Table 3.3.3. Witness questionnaire: PNES (#6) vs. ES (#10): list of all variables with sensitivity or specificity above pre-set threshold.

Question	Variable	PNES			ES			SE	SP	p-value
		Present	Absent	Not indicated	Present	Absent	Not indicated			
24/47/70	Side-side head movements in at least one of the witnessed seizures	4	2	-	0	9	1	66.7	100	0.0110
25/48/71	Ictal eye closure in at least one of the witnessed seizures	4	2	-	0	9	1	66.7	100	0.0110

Legend: PNES psychogenic non-epileptic seizures; ES epileptic seizures; SE sensitivity; SP specificity.

Table 3.3.4. Witness questionnaire. PNES (#6) vs. ES (#10): list of all variables with both sensitivity and specificity no less than 50% and sensitivity or specificity between 60 and 80 (below the pre-set threshold).

Question	Variable	PNES			ES			SE	SP	p-value
		Present	Absent	Not indicated	Present	Absent	Not indicated			
19/42/65	On/off shaking or stiffening	3	3	.	1	9	.	50.00	90.00	0.1181
22/45/68	Being “talked out” of seizures	2	2	2	3	6	1	50.00	66.67	1.0000
28/51/74	Breathing pattern (Ictal)	3	3	.	4	6	.	50.00	60.00	1.0000
30/53/76	Sudden fall (Ictal)	3	2	1	3	6	1	60.00	66.67	0.5804

Legend: PNES psychogenic non-epileptic seizures; ES epileptic seizures; SE sensitivity; SP specificity.

4. STUDY OF THE CHARACTERIZATION OF THE DIAGNOSIS OF IDIC(15) SYNDROME

Abstract

Idic(15) syndrome, is a rare neurogenetic disorder resulting from several genetic mechanisms the most frequent of which is a supernumerary marker chromosome 15. The disease is characterized by an unspecific phenotype, clinical heterogeneity and wide range of severity. The aims of this project were: 1. The identification of symptoms, signs and instrumental findings, singly or in various combinations, favoring the early diagnosis of the idic(15) syndrome; 2. The correlation of the clinical and instrumental findings to the diagnosis; 3. The characterization of the diagnosis of the idic(15) syndrome; 4. The assessment of extent to which epilepsy can be considered a characteristic feature of the disease.

Another important aim was to verify the identification and detection of specific signs or symptoms by different experts in a homogeneous and objective way.

32 patients (16 cases and 16 controls), age and sex matched, were enrolled and 5 raters blind to the diagnosis revised the patients information in three different steps: 1. Clinical charts review; 2. Video of neurological examination and patients' behaviour; 3. Instrumental tests examination (EEG, MRI, CT-Scan). Control patients were subjects with different neurodevelopemental disorders that fell in the differential diagnosis recruited from the same settings as the patient group.

Variables easily recognized in patients by raters with a good agreement (>0.6, calculated with Kendall's coefficient W) where almost the same of those described by Battaglia (2008), but high scores of SE and SP were found only for hypotonia and feeding difficulties in the newborn period. When considering these two variables as present in the same patients, SP increased to 87.5 and SE decreased to 36.3. These two variables, when combined, help to discriminate only to some extent idic(15) syndrome from other neurodevelopemental

disorders: 76% of patients with these signs have the disease and 64% of patients without these signs cannot be diagnosed with idic(15) syndrome. Analysing the results reported in the three steps by the raters, step 1 and 2 made a greater contribution to the correct diagnosis than step 3. EEG, MRI and CT-Scan deviated raters from a correct differential diagnosis probably because the results of instrumental investigations reflect a subjective interpretation of the electrophysiological and imaging findings.

4.1 Introduction

The idic(15) syndrome has received little attention because of its rarity, the fairly unspecific phenotype, the clinical heterogeneity, and the wide spectrum of severity. Although attempts have been made to identify common clinical features (hypotonia, developmental delay/intellectual disability, autistic behaviour, and epilepsy) (Battaglia, 2008), no formal characterization has been attempted with the intent to select clusters of symptoms, signs and laboratory/instrumental tests, which could be used in the differential diagnosis with other neurodevelopmental disorders characterized by mental retardation, intellectual disability, epilepsy, and altered behaviour. The contribution to the diagnosis of individual symptoms and/or signs and their combinations could not only favor an early diagnosis of the idic(15) syndrome, but could also help defining any genotype-phenotype correlation and are a valuable reference for epidemiological studies.

4.1.1. The phenotype and genotype of idic(15) syndrome

idic(15) syndrome is a rare neurogenetic disorder resulting from several genetic mechanisms the most frequent of which is a supernumerary marker chromosome 15, also known as Inv Dup (15) - Idic(15) -Tetrasomy 15q, with an incidence at birth of approximately 1 in 30,000 and an almost equal distribution in males and females (Battaglia, 2008). Interstitial 15q11-13 duplications and triplications have been less frequently described (Repetto et al, 1998; Schinzel et al, 1994). The prevalence of chromosome 15q11-13 duplications is estimated in

1 in 600 patients with developmental delay (Piard et al, 2010). Both Inv Dup (15) and interstitial 15q11-13 duplication are included in a broad clinical phenotypic spectrum (Rocha et al, 2012). A case of mosaicism for Inv Dup (15) in an adult healthy man was also described (Guanciali-Franchi et al, 2008).

The main clinical features consist of early central hypotonia, joint hyperlaxity, short stature, developmental delay, intellectual disability, impairment of verbal expressive language, autistic-like behaviour, epilepsy with a wide variety of seizure types and interictal EEG abnormalities. Feeding difficulties are reported in the newborn period and recurrent upper respiratory tract infections during infancy. Minor dysmorphisms are absent or subtle: high forehead, frontal bossing, epicanthal folds, deep set eyes, downslanting palpebral fissures, synophrys, low-set and posteriorly rotated ears, broad nose, short philtrum, anteverted nares, midface hypoplasia, large incisors, cleft palate/highly arched palate, clinodactyly, syndactyly, brachydactyly. Occasionally major malformations are described: ventricular septal defects, tetralogy of Fallot, unilateral renal agenesis, umbilical and inguinal hernias. Microcephaly occur in less than 20% of individuals, macrocephaly in less than 3% (Battaglia, 2005; Ouldim et al, 2007; Hou and Wang, 1998; Buoni et al, 2000). Developmental delay and intellectual disability may have a different level of severity, from mild to profound (Hou and Wang, 1998).

Behavioural phenotypes range from gaze avoidance or anxiety or emotional lability to pronounced autistic-like features including absent expressive language, poor intention to communicate, echolalia, and stereotypies (hand-flapping, hand-clapping, etc.) (Battaglia et al, 2008).

Epilepsy is frequent in this syndrome, but some patients have no history of seizures. Seizure onset can occur from infancy, often with infantile spasms (Valente et al, 2006), but also in childhood or even in adulthood with focal or generalized seizures types (Chifari et al, 2002). A wide variety of seizure types has been described even in the same patient, among which

epileptic spasms, generalized tonic/tonic-clonic seizures; axial tonic seizures; atypical absences and myoclonic absence-like seizures (Takeda et al, 2000; Elia et al, 1998; Baker et al, 1994). In some patients, a diagnosis of Lennox-Gastaut syndrome has been made (Rocha et al, 2012). Sexual abnormalities were also described, including hypospadia, cryptorchidism and precocious puberty (Buoni et al, 2000; Grosso et al, 2001).

The idic(15) syndrome has a complex molecular characterization. The 15q11-q13 region is characterized by high instability, caused by the presence of several paralogous segmental duplications (Low Copy Repeats: LCRs) driving by Non Allelic Homologous Recombination (NAHR). NAHR occurring between these LCRs led to the delineation of 5 breakpoint regions (BP1 to BP5) (Pujana et al, 2002). Moreover, the region has a complex pattern of imprinting with at least five paternally expressed genes (MKRN3, MAGEL2, NDN, C15orf2, snoRNAs and SNRPN-SNURF) and two maternally expressed genes (UBE3A and ATP10A). The PraderWilli (PWS) syndrome/Angelman syndrome (AS) critical region is located between BP2-BP3. Maternal and paternal deletion of these regions is associated with AS and PWS in about 70% of the patients affected by one of these conditions with the deletion occurring between BP1 and BP3 (type I) in 40% of the cases, and between BP2 and BP3 (type II) in the remaining 60%. The deletion is the result of either an inter- or an intrachromosomal rearrangement (Carrozzo et al, 1997). Type I deletion shows more severe phenotypes than type II (Roberts et al, 2002). More recently, deletions involving BP3-BP5 or BP4-BP5 have been reported in association with a wide phenotypic variability of abnormalities ranging from intellectual disability, schizophrenia, autism, and 1% of idiopathic generalized epilepsy (van Bon et al, 2009).

Duplication of the 15q11-q13 region occurs in two contexts: a complex genomic rearrangement resulting in the presence of a supernumerary marker chromosome visible on standard karyotype that is constituted by an inverted duplication (invdup(15) or isodicentric

chromosomes (idic(15)) or an interstitial duplication (Wang et al, 2004) which can only be detected by molecular cytogenetics.

Supernumerary marker chromosome (SMC) derivative of chromosome 15 represents about 50% of the SMCs observed in humans (Crolla et al, 2005). Two-thirds of the invdup(15)s had a breakpoint beyond the standard distal PWS/AS deletion breakpoint BP3 (Roberts et al, 2003; Leana-Cox et al, 1994) whether smaller size SMCs do not contain the PS/AS region and have a breakpoint at BP2. Early molecular studies showed that the majority of the SMC(15)s have asymmetrical breakpoints, with the two inverted arms of the SMC being unequal in length with an unexpected level of complexity and heterogeneity that is not seen in other chromosome 15 rearrangements, such as deletions and duplications. This suggests that multiple mechanisms are involved in the formation of large SMC(15)s (Crolla et al, 2005; Roberts et al, 2003; Leana-Cox et al, 1994) including post-zygotic ones (Rossi et al, 2012). The majority of invdup(15) is of maternal origin, and could be associated with advanced maternal age. This sex difference is not explained, although several hypotheses have been suggested: NAHR does not occur in paternal gametogenesis, most affected fetuses are not viable, or the duplication remains undetected because carriers have normal phenotype (Battaglia et al, 2010).

The idic(15) syndrome has a remarkable phenotypic and genetic variability. Based on the present knowledge, there are few studies on the genotype-phenotype correlation and most 15q11q-13 duplications were studied by fluorescence in situ hybridization (FISH), that does not allow to detect submicroscopic copy number change and the exact chromosome breakpoints.

To the best of our knowledge, this study would be the first formal diagnostic investigation of the idic(15) syndrome, aimed to detect, in relation to the exact extent of duplication and to the genes involved, clinical, neurological, behavioural and electroencephalographic markers for the early diagnosis.

4.1.2 Background and objectives

The present study has been originated by a specific interest of the lay association "NonSolo15", represented by the family members of individuals with idic(15) syndrome, their caring physicians, and people interested in the knowledge and care of the disease. The association includes a total of 30 families, some of them actively interacting with the Dup15q Alliance (a twin association in the United States) with the inclusion of their cases in the US national registry. In each family, the patient with idic(15) syndrome has been the object of an intensive clinical and genetic investigation.

In the attempt to improve the knowledge of the disease and advance the diagnostic and therapeutic work-up, a particular interest arose on the need to establish a national registry of the disease. Soon it became evident that, given the present knowledge of the phenotypic aspects of the disease, a more accurate investigation of the clinical, laboratory and instrumental features and their correlation with the genetic pedigree was needed. Based on the results of the characterization study, the combination of symptoms, signs and other diagnostic findings with the best discriminatory power at different ages would be used as a valuable instrument for an early diagnosis of the idic(15) syndrome in clinical practice and for the screening of the disease upon activation of a population-based registry in well-defined small to medium size geographic areas.

In this project we planned to validate the diagnosis made by child neurologists based on symptoms, signs and instrumental findings comparing a cohort of patients of differing age and sex with confirmed diagnosis of idic(15) syndrome to patients usually considered in the differential diagnosis as having intellectual disability, functional impairment, and behavioural abnormalities in various combinations. Specific aims include:

1. The identification of symptoms, signs and instrumental findings, singly or in various combinations, favoring the early diagnosis of the idic(15) syndrome;

2. The correlation of the clinical and instrumental findings to the diagnosis;

3. The characterization of the diagnosis of the idic(15) syndrome;

4. The assessment of extent to which epilepsy can be considered a marker of the disease.

The primary objective of the study is the identification of symptoms, signs and instrumental findings, singly or in various combinations comparing patients with idic(15) syndrome to patients with other neurodevelopmental disorders considered in the differential diagnosis. The research question to be addressed is that idic(15) syndrome differs from other neurodevelopmental disorders in a number of symptoms and/or signs whose combination defines a peculiar clinical phenotype.

Another important aim was to verify the significance to identify and detect a single sign or symptoms by different experts in a homogeneous and objective way.

4.2 Methods

The study population was represented by 16 patients of all ages and either sex with idic(15) syndrome (the cases) and 16 patients (the controls) with other diseases involved in the differential diagnosis. The differential diagnosis involves other neurodevelopemental disorders characterized by intellectual disability, autism, abnormal behavior, functional impairment. The cases were mostly recruited among the members of the association "NonSolo15" and the controls were patients followed by child neurologist of the participating centers. The diagnosis of each clinical condition was the one made by the caring child neurologist and was based on the results of clinical, laboratory and instrumental tests (including genetic tests) and was selected as the gold standard. After releasing a written informed consent, the family members (or other legal representatives) of eligible cases and controls permitted the diagnostic assessment of the affected individuals, including the accession to the patients' medical records. For each individual included in the study, an accurate history was taken from a key informant. The patient underwent a full clinical investigation (including the neurological examination, the assessment of spontaneous

behaviour and his/her basic interactions with the examiner). History and clinical assessment were video-recorded in the caring physician's office.

Video-recordings and all the material included in the patients' medical records (except for the results of the genetic tests) were examined by a commission of experts represented by 5 child neurologists, chosen among those actively involved in the management of neurodevelopmental disorders. The experts (the raters) were blind to the diagnosis. Each rater was asked to make the diagnosis (idic(15) syndrome vs. other) indicating, for each diagnosis, the degree of diagnostic certainty (as definite, probable or uncertain) in three subsequent steps, the first after reviewing the medical records (deprived of the information obtained from the laboratory and instrumental tests), the second after examining the video-recordings, and the third after examining the results of the laboratory and instrumental tests. At each step, a separate section of an e-CRF (see the Appendix) was filled.

When all the tasks have been accomplished by the raters, the inter-rater agreement was tested.

At the end of the study, a cluster of symptoms, signs and laboratory/instrumental findings were tentatively identified to help the caring physician to make an early diagnosis of idic(15) syndrome in a child or young adult with developmental delay, intellectual disability, epilepsy and behavioural disturbances in various combinations. Symptoms, signs and laboratory values were assessed comparing the phenotype of cases and controls.

The identification of diagnostic criteria with differing degree of certainty helped the screening of patients affected by idic(15) syndrome among those with neurodevelopmental disorders in a given population at risk.

4.2.1 History taking and physical examination

A detailed history on the disease onset and course was collected through examination of the patient’s medical records and direct interview of the parents or legal representatives. The records were anonymized and deprived of any detail likely to uncover the final diagnosis.

The following data were collected: date of birth, sex, family history, current weight, height and cranial circumference, gestational week at delivery, Apgar score, weight, length and cranial circumference at birth, feeding difficulties in the newborn period, age at standing, walking and first words, number of current words, age at onset of self-feeding and playing (where possible), presence of recurring URI, constipation, hypogonadism, urinary tract defects, congenital heart defects, unilateral renal agenesis, inguinal and/or umbilical hernias.

The following major and minor malformations were actively searched: growth restriction, microcephaly, macrocephaly, flat occiput, occipital groove, high forehead, frontal bossing, epicanthal folds, deep set eyes, downslanting palpebral fissures, synophrys, low-set and posteriorly rotated ears, broad nose, short philtrum, anteverted nares, midface hypoplasia, large incisors, cleft palate/highly arched palate, protruding tongue, drooling, prognatia, wide mouth, wide spaced teeth, hypopigmented skin (compared to family), light hair color (compared to family), light eye color (compared to family), hyperactive lower extremities, uplifted, flexed arms during ambulation. The presence of obesity was also investigated.

A number of neurological signs were searched: hypotonia, wide-based gait with pronated or valgus-positioned ankles, ataxia, clumsiness, jerky motions, tremor, swallowing disorders, strabismus, brisk deep tendon reflexes, increased sensitivity to heat, abnormal sleep-wake cycles, developmental delay (mild, moderate severe), mental retardation.

Psychiatric signs were also investigated: laughter/smiling, happy demeanor, easy excitement, echolalia, hand-flapping movements, hypermotoric behaviour, tantrums, stubbornness, verbal perseverance, skin picking, hyperphagia, anxiety, emotional lability, impulsivity, aggressiveness.

Epilepsy, where present, was specifically investigated: seizure types, response to treatment, EEG findings. The presence of autistic behaviour was also investigated using the ADOS inventory (Battaglia et al 2008, Lord et al 2006).

4.2.2 Patient interview and examination

A standardized video-recorded interview was performed in all cases and controls. The interview included the general and the neurologic examination, and a number of spontaneous and ordered activities required to assess the level of age-related self-sufficiency of the patient during daily living activities. Special attention was paid to the detection of the same major and minor malformations (if any) enlisted in the previous paragraph (history taking and physical examination) and the degree of functional impairment.

Videos were accessed by the rater along with the medical records and the results of the laboratory and instrumental tests.

4.2.3 Collection of reports of instrumental examinations (EEG, MRI, CT-SCAN)

All instrumental examinations present in the medical records were identified and the results reported. Reports were also classified into normal, non-specific, and abnormal.

On the basis of the history, the clinical findings, and the results of the laboratory and instrumental examinations, a diagnosis were tentatively made by each rater choosing one of the categories below:

1. Idic(15) Syndrome
2. Angelman Syndrome
3. Pitt-Hopkins Syndrome
4. Mowat-Wilson Syndrome
5. Mucopolysaccharidosis type 3
6. FOXG1 Syndrome
7. West Syndrome
8. Autism spectrum disorder
9. Other neurodevelopmental disorder (to be specified)

The level of diagnostic accuracy (definite, probable, uncertain) were also indicated.

4.2.4 Data collection

Data, video-recorded interviews and instrumental examinations were collected in the "Unità Operativa Semplice di Epilettologia e neurofisiologiaclinica – Unità per le Gravi Disabilità in Età Evolutiva (UGDE) - Conegliano - Pieve di Soligo (TV)" and in the "U.O.C. di Neurologia e Neurofisiopatologia Clinica e Strumentale IRCCS "Associazione Oasi Maria SS" Troina (EN)" and sent to the raters for the characterization of the diagnosis. Information about history, video-recorded interviews and instrumental examinations were blind and sent anonymously to the raters who filled ad-hoc comprehensive check-list reported in the e-CRF (see the Appendix).

4.2.4.1 Database management and quality control

Study data were collected and managed in a web-based password-protected platform hosted at IRCCS – Mario Negri Institute for Pharmacological Research, Milan. Access details were provided to the raters in order to entry the data in the ad-hoc comprehensive e-CRF and validate the diagnosis.

4.2.5 Statistical methods and data analysis

When all the tasks were accomplished by the raters, the inter-rater agreement was tested at different levels using the Kendall's coefficient of concordance (W) on the following groups: 1. The diagnosis of idic(15) syndrome vs. other clinical condition, in general and by degree of diagnostic certainty; 2. For each symptom, sign and instrumental finding separately. Kendall's W takes values from 0 (no agreement) to 1 (perfect agreement).

Symptoms, signs and instrumental findings with Kendall's W higher than 0.6 were evaluated in terms of SE and SP to assess the ones able to predict the diagnosis of idic(15). Either SE or SP must be at least 60%. Each raters examined charts and videos of all cases and all controls, giving a total of 160 interviews (80+80).

4.2.6 Regulatory and ethical compliance

This study was planned and performed according to the principles of Good Clinical Practice (ICH-GCP), the declaration of Helsinki and national laws and regulations about clinical studies. The approval of the Independent Ethics Committees (IEC) of the recruiting centers were obtained before the beginning of the study. Eligible patients and controls were included in the study after releasing written IEC-approved informed consent, or, if incapable of doing so, after such consent was provided by a legally acceptable representative.

4.3 Results

4.3.1 Patients

A total of 32 patients were enrolled, 16 cases with a diagnosis of idic(15) syndrome and 16 controls with the following diagnoses: 5 Angelman syndrome; 2 Rett syndrome; 2 autism spectrum disorders; 2 Dravet syrome; 2 epileptic encephalopathies in FOXG1 syndrome; 1 epileptic encephalopathy; 1 Pitt-Hopkins syndrome; 1 pervasive developemental disorder.

Table 4.1 shows the description of the sample and table 4.2 the comparison, by sex, of birth weight, length at birth and head circumference between cases, controls and standard values for WHO (who.int/childgrowth/en). No differences were found between cases and controls.

4.3.2 Concordance

The coefficient of concordance (Kendall's coefficient W) for the diagnosis of idic(15) syndrome at step 1 was 0.43 ($p<0.0001$); at step 2 was the same (0.43; $p< 0.0001$); at step 3 was 0.31 ($p= 0.0143$).

Table 4.3 includes the signs and symptoms identified in step 1 and 2 with $W>0.6$ for cases and controls specifying whether each variable was present or absent in either group along with SE and SP. In step 3, no signs and symptoms were found to have $W>0.6$.

Only two of these variables met the pre-set criteria of high SE and SP: feeding difficulties in the new-born period and hypotonia. When considering the presence of both signs in the same patient, SP increased to 87.5 and SE decreased to 36.3. The positive predictive value was 76.3 and the negative predictive value was 64.2. Epilepsy was found to have a W of 0.84 but was evenly distributed between cases and controls.

Comparing cases with interstitial 15q11-13 duplication (n=7) and Inv Dup (15) tetrasomy (n=9) the only variables significantly different between these two groups were: congenital heart defects, macrocephaly, high forehead, downslanting palpebral fissures, drooling, scoliosis, easy excitability, skin picking, aggressiveness, large incisors, wide spaced teeth, joint hyperlaxity, slow waves at EEG. However, for all these variables, the W concordance coefficient was lower than 0.60.

4.3.3 Degree of diagnostic accuracy

Table 4.4 reports the degree of accuracy of the diagnosis (No, Uncertain, Probable, Yes) for all raters for 80 observations among cases and 80 among controls (each patient being considered as many times as the number of raters). Considering the single answers, the No answers in the control group decreased from 57.5% to 55.0% from step 1 to step 2 and increased to 57.5% at step 3; the Uncertain answers increased from 16.3% to 22.5%; the Probable answers decreased from 22.5% to 17.5%; the Yes answers decreased from 3.8% to 2.5%. In the case group, the No answers increased from 26.5% to 32.5%; the Uncertain answers increased from 16.3% at step 1 to 21.3% at step 2 and decreased to 16.3% at step 3; Probable answers remained the same at step 1 (46.3%) and 2 (47.5%) and decreased at step 3 (38.5%); the Yes answers decreased from 11.3% (step1) to 6.3% (step 2) and then increased at 12.5% at step 3.

4.4 Tables

Table 4.1. Description of the sample

	Cases		Controls	
	N	**%**	**N**	**%**
Sex				
F	8	50.0	8	50.0
M	8	50.0	8	50.0
	Median	**IQR**	**Median**	**IQR**
Age	9.5	6.5-12.0	9.5	6.5-12.5
Gestational age	40.0	38.0-40.0	39.0	38.0-40.0
Weight at birth	3.2	2.8-3.4	3.3	2.7-3.4
Length at birth	49.8	46.5-51.0	50.0	49.0-52.0
Head circumference	34.0	32.5-35.5	34.0	33.0-34.5
Apgar score	9.0	8.0-9.0	9.0	9.0-9.0

F, females; M, males; IQR, interquartile range.

Table 4.2. Comparison of variables at birth between cases, controls and standard values

	Females		Males	
	Median	**IQR**	**Median**	**IQR**
Standard values				
Weight	3.2	2.9-3.6	3.3	3.0-3.7
Length	49.1	47.9-50.4	49.9	48.6-51.2
Head circumference	33.9	33.1-34.7	34.5	33.6-35.3
Cases				
Weight	3.0	2.2-3.4	3.3	2.9-3.5
Length	50.0	44.4-50.0	49.5	47.0-52.0
Head circumference	33.0	31.0-35.5	34.0	33.5-35.0
Controls				
Weight	3.0	2.3-3.4	3.3	3.3-3.5
Length	49.5	47.0-50.0	52.0	50.0-53.0
Head circumference	33.2	30.0-34.5	35.0	34.0-37.0

IQR, interquartile range.

Table 4.3. Variables with Kendall's W higher than 0.6

Variabili	W	Cases			Controls			SE	SP	p-value
		No	Yes	Unknown	No	Yes	Unknown			
STEP 1										
Feeding difficulties in the newborn period	0.62	22	49	9	54	24	2	69.0	69.2	<0.0001
Standing	0.83	12	62	6	10	68	2	83.8	12.8	0.55
Walking	0.88	12	66	2	10	70	0	84.6	12.5	0.60
Speech	0.69	41	38	1	43	37	0	48.1	53.8	0.82
Self feeding	0.62	35	25	6	39	53	2	52.7	32.1	0.05
Overall judgement of developmental delay (severe vs. moderate/mild/no)	0.65	19	52	2	24	50	1	73.2	32.4	0.63
Epilepsy	0.84	19	52	9	24	50	6	73.2	32.4	0.47
Infantile spasms	0.61	42	16	22	48	6	26	27.6	88.9	0.03
STEP 2										
Obesity	0.62	79	0	1	66	14	0	0.00	82.5	<0.0001
Hypotonia	0.65	22	41	17	50	20	10	65.1	71.4	<0.0001
Overall judgement of developmental delay (severe vs. moderate/mild/no)	0.69	51	29	0	45	35	0	36.3	56.3	0.33
Feeding difficulties in the newborn period + hypotonia	0.63	39	29	12	70	9	1	36.3	87.5	<0.0001

W, Kendall's W; SE, sensitivity; SP, specificity.

Table 4.4. Degree of diagnostic accuracy

	Step 1		Step 2		Step 3	
idic(15) Diagnosis	**Case N (%)**	**Control N (%)**	**Case N (%)**	**Control N (%)**	**Case N (%)**	**Control N (%)**
No	21 (26.25)	46 (57.50)	20 (25.00)	44 (55.00)	26 (32.50)	46 (57.50)
Uncertain	13 (16.25)	13 (16.25)	17 (21.25)	17 (21.25)	13 (16.25)	18 (22.50)
Probable	37 (46.25)	18 (22.50)	38 (47.50)	16 (20.00)	31 (38.75)	14 (17.50)
Yes	9 (11.25)	3 (3.75)	5 (6.25)	3 (3.75)	10 (12.50)	2 (2.50)

5. PREVALENCE, PROGNOSIS AND ANTIEPILEPTIC DRUG RETENTION OF EPILEPSY IN A WELL-DEFINED POPULATION OF NORTHERN ITALY (EPIRES STUDY)

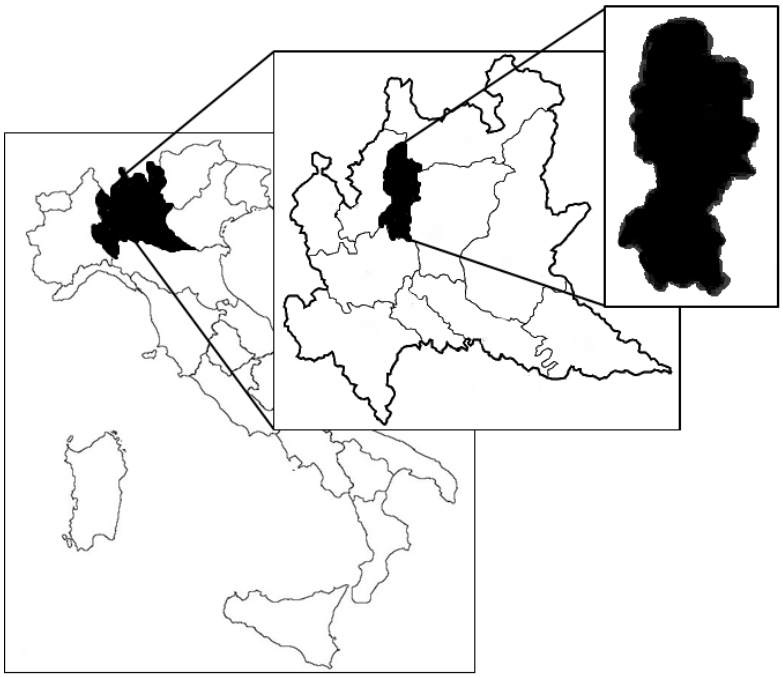
The next study provides added value to the knowledge of the epidemiology, prognosis and treatment of drug-resistant epilepsy in Italy, by investigating the long-term outcome of patients not responding to two or more antiepileptic drugs (Kwan et al, 2010)) and providing the practising physicians with instruments to test treatment efficacy in clinical practice. Three manuscript have been published about this topic:

- Giussani G, Canelli V, Bianchi E, Franchi C, Nobili A, Erba G, Beghi E; EPIRES Group. A population-based study of active and drug-resistant epilepsies in Northern Italy. Epilepsy Behav 2016;55:30-7.

- Giussani G, Canelli V, Bianchi E, Erba G, Franchi C, Nobili A, Sander JW, Beghi E; EPIRES Group. Long-term prognosis of epilepsy, prognostic patterns and drug resistance: a population-based study. Eur J Neurol 2016;23:1218-27.

- Giussani G, Bianchi E, Canelli V, Erba G, Franchi C, Nobili A, Sander JW, Beghi E, and the EPIRES Group. Antiepileptic drugs discontinuation by people with epilepsy in the general population. Epilepsia 2017, in press.

Fig.5. Map of the study area: district of Lecco, Lombardy, Northern Italy.



Abstract

The aims of the study were: 1. To calculate the prevalence of active epilepsy and DRE in a cohort of patients from a well-defined geographic area, using as reference the ILAE definition; 2. To calculate the proportion of incident cases developing DRE; 3. To assess seizure outcome (and prognostic patterns) in a community-based cohort of people with epilepsy; 4. To identify prognostic indicators among selected demographic and clinical factors; 5. To define the outcome of epilepsy and the prognostic patterns of people with DRE ILAE 2010 definition compared with the rest of the cohort; 6. To estimate the retention rate of AEDs according to the order of administration (first, second, or subsequent) in general and by drug; 7. To investigate the reasons for stopping AEDs with reference to the sequence of drug assignment; 8. To ascertain possible predictors of treatment discontinuation with reference to the commonest reasons for discontinuing the assigned drug.

The study population (146,506; year 2008) resided in the province of Lecco, Northern Italy. The medical records of 123 general practitioners were reviewed to identify patients with epilepsy diagnosed by a neurologist during the period 2000-2008. The point prevalence of active epilepsy and DRE were calculated on December 31 2008. Remission was defined as uninterrupted seizure freedom lasting 2 years or longer. Prognostic patterns were early remission, late remission, remission followed by relapse, no remission. Cumulative probabilities of AED withdrawal for specific reasons were estimated using cumulative incidence functions. The probabilities of withdrawing for terminal remission, or of achieving sustained remission while still on treatment, were also evaluated. Sex, age at diagnosis, seizure types, duration at diagnosis and syndrome were assessed with hazard ratios (HR) and 95% confidence intervals (95% CI).

The sample included 747 prevalent patients with epilepsy, 684 with active epilepsy, and 342 incident cases. DRE was 15.6% (107/684) of all active epilepsies and 10.5% (36/342) of incident cases. Point prevalence was 0.73 per 1,000. Standardized prevalence of DRE was 0.7 per 1,000 (Italian population) and 0.8 per 1,000 (World population).

428 (59%) patients were seizure-free. The probability of achieving 2-year remission was 18% at treatment start, 34% at two years, 45% at five, 52% at ten and 67% at 20 years (terminal remission, 60%). Epilepsy syndrome and drug resistance were the only independent predictors of 2- and 5-year remission. Early remission was seen in 101 people (19%), late remission in 175 (33%), remission followed by relapse in 85 (16%), and no remission in 166 (32%). Treatment response was the only variable associated with differing prognostic patterns.

In this sample, the three commonest drugs were valproate, carbamazepine and phenobarbital. Reasons for AED withdrawal were, in decreasing order, terminal remission, ineffectiveness and adverse events. The probability of withdrawing the first AED for terminal remission was 1.0% at one year and increased to 20.0% at twenty years. Corresponding rates for

ineffectiveness were 2.9% and 12.6%; and for adverse events 0.5% and 3.3 %. Reasons for withdrawal varied with age, sex, disease characteristics, and drugs.

These data indicate that 1/6 patients with active epilepsy in the general population has DRE and 1/10 patients with newly diagnosed epilepsy will develop DRE within nine years from the diagnosis. Furthermore, the long-term prognosis of epilepsy is favourable in most cases. Early seizure remission is not invariably followed by terminal remission and seizure outcome varies according to specific patterns. Prolonged seizure remission and prognostic patterns can be predicted by broad syndromic categories and by the failure of two antiepileptic drugs. The initial AED given was retained in the majority of cases. Terminal remission, lack of efficacy and adverse effects were, in decreasing order, the commonest reasons for AED discontinuation. Withdrawal could be predicted by age at diagnosis, sex and clinical characteristics and varied among drugs.

5.1 Introduction

5.1.2 Drug-resistant epilepsy

As decribed above, DRE has been variously defined in published reports but in 2010. The ILAE issued a new definition of DRE (Kwan et al, 2010) and no studies have as yet been done to assess the frequency of DRE in well-defined populations conforming to this definition.

5.1.3 Prognosis of epilepsy

Epilepsy has a high potential for seizure remission. Studies in well-defined populations with newly diagnosed epilepsy have consistently shown a 1-year remission in up to 95% of people (Annegers et al, 1979; Sillanpää and Schmidt, 2006; Berg et al, 2015; Lindstene et al, 2001; Camfield et al, 2010; Camfield et al, 2013; Nicoletti et al, 2009; Wakamoto et al, 2000) and up to 71% are in remission at last observation with or without drugs (Annegers et al, 1979; Sillanpää and Schmidt, 2006; Berg et al, 2015; Wakamoto et al, 2000; Goodridge and

Shorvon, 1983; Geerts et al, 2010). A few studies have investigated the timing and outcome of prolonged periods of seizure freedom (the so called prognostic patterns) (Sillanpää and Schmidt, 2006; Berg et al, 2015; Goodridge and Shorvon, 1983; Geerts et al, 2010; Shorvon and Sander, 1986; Neligan et al, 2011; Brodie et al, 2012). These studies show that early remission predicts favourable long-term outcomes. Some who fail to achieve early remission can, however, still enter remission during the course of the condition; some who experience early remission may relapse and eventually fail to achieve further remission while others may again become seizure-free. Factors including the presence of a neurological disability (Berg et al, 2015; Wakamoto et al, 2000; Cockerell et al, 1997), aetiology (Annegers et al, 1979; Sillanpää and Schmidt, 2006; Nicoletti et al, 2009; Geerts et al, 2010), seizure type (Annegers et al, 1979; Nicoletti, et al, 2009), high seizure frequency before treatment (Wakamoto et al, 2000) and during the first months after treatment start (Geerts et al, 2010; MacDonald et al 2000), age at diagnosis (Annegers et al, 1979), disease duration (MacDonald et al, 2000), number of antiepileptic drugs (AEDs) used (Wakamoto et al 2000), and selected epilepsy syndromes (Sillanpää and Schmidt, 2006; Wakamoto et al 2000) are positive or negative predictors of remission. Age *per se* does not influence the prognosis of the disease, but epilepsy syndromes thought to have differing prognostic significance vary between children and adults (Berg et al, 2010).

This complex picture is the background against which the recent definition of DRE (Kwan et al, 2010) must be assessed.

5.1.4 Retention of AEDs

The response to AEDs is an important indicator of the prognosis of epilepsy. AEDs are generally efficacious in controlling seizures. In clinical practice, seizure freedom is seen in about 50% of people with previously untreated epilepsy (Annegers et al, 1979; Sillanpää and Schmidt, 2006; Kwan and Brodie, 2001). In people who do not respond to the first AED, the use of a second drug leads to complete seizure control in a lower proportion of cases and

there is a further decrease with each subsequent treatment change (Brodie et al, 2012; Berg et al, 2009; Berg et al 2006; Schiller et al, 2009). If the first drug fails, however, seizure-free rates vary across studies and, although DRE has been defined as the failure of two appropriate AEDs (Kwan et al, 2010), there are reports of people achieving seizure freedom even after having failed several AEDs (Berg et al, 2009; Luciano and Shorvon, 2007; Callaghan et al, 2007; Neligan et al, 2012). While withdrawal of ineffective drugs, when given as first or subsequent treatments, is usually clearly documented, the information becomes fragmentary regarding the reasons for discontinuation. Additionally, with some exceptions (Lhatoo et al, 2001; Wang et al, 2006; Huang et al, 2014), AED retention has not been assessed in a population-based sample. Lastly, there are no data on the history of AED treatment in samples of children and adults with epilepsy from the same population and followed for a prolonged period of time.

5.2 Aims of the study

1. To calculate the prevalence of active epilepsy and DRE in a population sample from a well-defined geographic area, using as reference the ILAE definition;

2. To calculate the proportion of incident cases developing DRE;

3. To assess seizure outcome (and prognostic patterns) in a community-based cohort of people with epilepsy;

4. To identify prognostic indicators among selected demographic and clinical factors;

5. To define the outcome of epilepsy and the prognostic patterns of people with DRE ILAE 2010 definition compared with the rest of the cohort;

6. To estimate the retention rate of AEDs according to the order of administration (first, second, or subsequent) in general and by drug;

7. To investigate the reasons for stopping AEDs with reference to the sequence of drug assignment;

8. To ascertain possible predictors of treatment discontinuation with reference to the commonest reasons for discontinuing the assigned drug.

5.3 Methods

The study was a retrospective, cross-sectional, non-interventional investigation extending over a nine-year period (January 1, 2000 – December 31, 2008). Patients with epilepsy residing in the province of Lecco were the study population. The local population is almost entirely of Caucasian origin (96%) and is fairly stable, with a migration rate of 3.3% for the year 2008 (emigration 1.2%; immigration 2.1%) according to the Italian Statistics Institute (ISTAT: http://demo.istat.it).

5.3.1 Health care provision in the study area

In Italy, primary care is administered free of charge by general practitioners (GPs) to all residents. Each GP follows up to 1,500 individuals. Essential medical information on each person is collected by the GP in electronic records that are made available to the new GP in the infrequent case that an individual with an established chronic condition joins his/her practice. Further details on the medical history (including treatments) are collected in electronic or paper records. Children and adolescents (ie, persons aged less than 18 years) and adults are assigned to two distinct GP categories having different education and background, according to the patient's needs. Except for age, the populations assigned to each GP are comparable in their demographic and socio-economic characteristics. As for other chronic diseases, epilepsy is entitled to receive free of charge all medical consultations, diagnostic aids and treatments for the detection and management of the disease. The exemption certificate is always released by a neurologist who has examined the patient, and confirmed the diagnosis. Through the exemption certificate the GP can have access to the diagnosis and all related diagnostic tests.

5.3.2. Sources of case ascertainment

A total of 263 GPs were active in the area during the study period. All were contacted and 123 of them (47%) volunteered to participate in the study. The GPs were requested to identify the medical records of all patients with seizures followed in their practice. These patients could be traced through diagnostic codes, EEG records, antiepileptic drug prescriptions, and disease-specific exemption codes. In addition, to ensure an accurate data collection, all GPs received a de-identified list of patients under their care with presumed diagnosis of epilepsy based on information contained in the database of the claims of health care services for the province of Lecco. This list was generated applying a validated algorithm including requests of EEGs and the prescriptions of drugs (Giussani et al, 2014; Franchi et al, 2013). All medical records of patients with epilepsy available in the GPs' office were reviewed by two trained junior investigators who interacted with the GP to confirm the diagnosis and exclude individuals not fulfilling the study's inclusion criteria. They also reviewed the records of patients assigned to the GPs but currently followed in other in- and out-patients facilities of the province (hospitals, nursing homes, ambulatory clinics).

When necessary, the same investigators called the neurologists (including those outside the study area) following the enlisted patients, to confirm the diagnosis or to complete the data needed to identify epilepsy syndrome and drug response.

5.3.3. Inclusion criteria and study definitions

Included were children, adolescents and adults fulfilling the diagnosis of epilepsy (ie. two or more unprovoked seizures 24+ hours apart), followed by the participating GPs, and residing in the area for at least one year during the study period. Excluded were patients with acute symptomatic seizures, neonatal seizures, single unprovoked seizures, and paroxysmal events other than epilepsy. In all cases, the diagnosis had been established through neurological consultation on the basis of clinical assessment prior the study, interictal EEG findings and, in some cases, brain neuroimaging (CT, MRI).

In keeping with the ILAE guidelines for epidemiologic studies in epilepsy (Commission, 1993), active epilepsy was defined as either being currently under treatment and/or having had at least one seizure in the previous five years. DRE was defined as the failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs (AED), as monotherapy or in combination, to achieve sustained seizure freedom (Kwan et al, 2010). In conformity with this definition, patients with DRE were identified as those in whom at least two AEDs had been discontinued for lack of efficacy or those in whom a third AED, either in combination or in substitution of the previous treatment, was prescribed. Adequacy of treatment was verified by two of us by reviewing all data available for each patient (see below). Drug plasma levels were not used to verify the appropriateness of treatment schedules.

Seizures and epilepsy syndromes were classified using the contemporaneous ILAE recommendations (Commission, 1981; Commission, 1989). The new classification of the epilepsies (Scheffer et al, 2017), not available during the study period, was not applied. As detailed information was not available in all cases, seizures and syndromes were classified using broad categories. Seizures were classified as focal, generalized or unclassifiable. Syndromes were classified as partial (idiopathic, symptomatic or cryptogenic), generalized (idiopathic, symptomatic/cryptogenic), undetermined and special.

5.3.4. Data collection

For each eligible case, the information was collected retrospectively until December 31, 2008, out-migration or death, whichever came first. The following data were collected anonymously: 1. Main demographics; 2. Seizure type(s), disease duration (from the first seizure to the diagnosis), epilepsy syndrome, duration of follow-up (from diagnosis); 3. Number and type of drugs including drug starting date, daily doses and changes, and timing of administration, withdrawal date or last follow-up date, whichever came earlier (see the

Appendix). The reasons for discontinuation of each drug were also collected; these included lack of efficacy, adverse events and poor tolerability, seizure freedom, or other (pregnancy, death, etc.). In rare instances, where the medical records were not sufficiently detailed on the duration of treatments, the history of treatments and health care utilization was collected from the administrative records that include details on when each drug was started and discontinued. Using these sources, all putative epilepsy cases were traced, relevant data on epilepsy were collected, and patients with active epilepsy and DRE were identified.

Seizure outcome and prognostic patterns were classified according to pre-selected definitions. Remission was a period of uninterrupted seizure freedom lasting 2 years or longer at any time after diagnosis. We investigated 2-year and 5-year remission periods. Sustained remission was defined as seizure remission for at least 2 years at any time after diagnosis and continuing until last follow-up. Terminal remission was defined as seizure remission for at least 2 years at last follow-up with or without previous seizure relapses. Prognostic patterns were defined as: 1. Early remission: 2-year seizure freedom starting within two years from treatment start which is sustained; 2. Late remission: 2-year remission starting more than two years after treatment start which is sustained; 3. Remission followed by relapse: early or late remission followed by relapse with/without terminal remission; 4. No remission: never entering 2-year remission during the entire follow-up.

5.3.5. Statistical analysis

Statistical analyses were performed using SAS (version 9.2; SAS Institute, Inc, Cary, NC, USA).

The prevalence of active epilepsy was calculated on December 31 2008. The population at risk was calculated as the total number of patients assigned to the participating GPs at the prevalence date. Incident epilepsy cases, a subset of the prevalent cases, were identified as those who received the diagnosis during the period 2000-2008.

Prevalence of DRE was calculated on December 31 2008 in the population at risk. Incident DRE cases were calculated as a subset of incident epilepsy cases. We also stratified point prevalence of epilepsy and DRE by age and sex. Ninety-five percent binomial confidence intervals (95% CIs) were calculated for prevalence. Prevalence was then standardized by the direct method to the Italian population, 2001 census (ISTAT http://demo.istat.it) and to the World population, mid-year 2000 (http://www.census.gov/cgi-bin/broker).

All descriptive statistics were reported as count and percentage. The variables analyzed were age, sex, type of seizures, epilepsy syndromes, disease duration, and duration of follow-up. Drug-resistant and non-drug-resistant patients were compared in both the prevalent and incident population and the differences were tested using the chi-square test. To identify predictors of drug resistance, multivariable logistic regression models were used, with DRE as dependent variable and age, sex, disease duration, duration of follow-up and epilepsy syndrome as covariates. The overall significance of the model and the goodness-of-fit were verified respectively with the Wald statistics and the Hosmer-Lemeshow test. The results are reported as odds ratios (ORs) with 95% CIs. The cumulative risk to become drug resistant in the incident population was estimated with the Kaplan Meier survival curves, first in the whole sample then separately by age classes, sex and epileptic syndrome. Survival curves were compared using the log-rank test and Sidak's adjusted pairwise comparisons. The association between each variable and DRE was also tested with univariate and multivariate Cox's proportional hazards function models. Proportionality assumption was verified including in the model time dependent covariates for each predictor. Results were reported as hazard ratios (HRs) and adjusted hazard ratios (adjHRs), with 95% CIs. The significance level was set at 0.05. As only few patients reported missing data, they were excluded from the analysis. Descriptive statistics for prognostic patterns are presented as frequencies, medians (with range), means (with standard deviations) or proportions, as appropriate. The cumulative time-dependent probability to achieve 2-year and 5-year remission, and to

achieve 2-year and 5-year terminal remission, was calculated in patients followed for at least two and five years respectively, using Kaplan-Meier curves comparing sex, age group at diagnosis, the main syndromic categories and those with or without DRE, using the log-rank test. Independent predictors of 2-year and 5-year remission (ever and terminal) were identified using the Cox multivariable proportional hazards function. Prognostic patterns were assessed in individuals with at least five years of follow-up, comparing all demographic and clinical variables with the Chi square test (or the Fisher exact test where required), followed by post-hoc step-down Šidák adjusted contrasts, comparing each category versus all other categories grouped together, within each prognostic pattern. Multivariable multinomial logistic regression models were used to correlate prognostic patterns with age, sex, disease duration, epilepsy syndrome, and number of AEDs. Statistical significance was set at the 5% level ($p<0.05$).

Descriptive statistics for AEDs withdrawal are presented as counts and percentages. Administration frequencies and cause-specific withdrawal frequencies were calculated for each active principle and by prescription order. AEDs were also grouped in two different classes: old and newer (marketed before and after 1990). Old drugs included barbexaclone (BSC), carbamazepine (CBZ), clobazam (CLB), clonazepam (CNP), ethosuximide (ESM), phenobarbital (PB), phenytoin (PHT), primidone (PRM), valproate (VPA), valpromide (VPM); newer drugs included gabapentin (GBP), levetiracetam (LEV), lamotrigine (LTG), oxcarbazepine (OXC), pregabalin (PGB), tiagabine (TGB), topiramate (TPM), vigabatrin (VGB), zonisamide (ZNS).

To account for competing risks, cumulative probabilities of AED withdrawal from specific causes over twenty years from treatment start were estimated using cumulative incidence functions. The cumulative probability of cause-specific AED withdrawal was calculated for the first, second, and third AED, for the most common AEDs (i.e. used by more than 100 people), and for new and old AEDs separately. Differences in the cumulative incidence

functions between new and old AEDs were assessed using Gray's test (Gray, 1988). For the first AED, the cumulative probability of withdrawing for terminal remission (ie, seizure freedom for at least two years at last follow-up) while still on treatment, was also evaluated. The association between drug discontinuation and sex, age at diagnosis (<15, 15-64, 65+ years), seizure types (focal, generalized, unclassifiable), duration from first seizure to diagnosis, and epilepsy syndrome (idiopathic, cryptogenic/symptomatic, special/undetermined) was assessed using univariable Cox proportional hazards models. Models for the most commonly used AEDs were adjusted for the number of previous drugs taken. Results were presented as Hazard Ratios (HR) with 95% Confidence Intervals (95%CI). Missing data were handled using the listwise deletion method.

5.3.6 Ethics and confidentiality

The study was approved by the Ethics Committee of the Provincial Hospital of Lecco (Register number: 2011-003428-11). Local Health Service authorization was obtained to collect anonymous data from the GPs. Where GPs needed to collect additional information from individuals, informed consent was obtained. All the data were managed according to the current Italian privacy rules.

5.4 Results

5.4.1 Prevalence of active epilepsy and DRE

The 123 participating GPs represented a population of 146,506 for the year 2008. Except for a slight predominance of children and a slight under-representation of elderly individuals, this population was fairly comparable to the entire population of the province of Lecco, as shown in Supplementary Table 5.1.

A total of 1,021 patients' charts were screened in the GPs' archives including thirty-four cases previously assigned to the GPs but living in nursing homes. After excluding other diagnoses, coding errors and duplicate records, a total of 747 patients (381 males) with

epilepsy and 684 patients with active epilepsy were identified (Figure 5.1). These patients have been followed for a total of 11,045.5 person-years (median, 9.5; interquartile range, 4.5-22.5).

The prevalence of active epilepsy (as of December 31 2008) was 4.67 per 1,000 (Table 5.1). The disease was slightly more prevalent in males and peaked in people aged 75 years or older.

Standardized prevalence of epilepsy was 4.8 per 1,000 (Italian population) and 4.5 per 1,000 (World population).

On December 31 2008, patients with prevalent DRE were 15.6% (n=107) of the entire population with active epilepsy (n=684), which translate into a prevalence of 0.73 per 1,000. DRE was more prevalent in women than in men at all ages except in the >75 years group where it was more prevalent in men (Table 5.2).

In the incident epilepsy population (n= 342) patients developing DRE during the period 2000-2008 were 10.5% (n=36).

Table 5.3 illustrates the main demographic and clinical characteristics of patients with DRE, as compared to non-drug-resistant patients. In the prevalent population, significant differences were found for sex, age and epilepsy syndrome: DREs was more prevalent in women than in men, in younger individuals and in patients with generalized cryptogenic/symptomatic or undetermined epilepsies (see also Supplemetary Table 5.2). In the incident population, significant differences between drug-resistant and non-drug-resistant patients were found only for age and epilepsy syndrome. These differences were confirmed by multivariable regression models, which also showed an increasing prevalence of DRE with increasing duration of follow-up (Table 5.4).

The cumulative risk to become drug-resistant among incident cases during the period 2000-2008 was 3.7% at 1 year from diagnosis, 6.5% at 3 years from the diagnosis, and 12.3% at 5 years from diagnosis (Figure 5.2). The mean estimated time to develop drug-resistance

was 5.6 years from diagnosis. A significant difference in the cumulative risk to develop drug-resistance was found for age and epilepsy syndrome, but not for sex (Figure 5.3, 5.4 and 5.5). Specifically, the cumulative risk to become drug-resistant was highest among patients less than 15 years old: 11.4% at 1 year, 17.8% at 3 years and 29.1% at 5 years from diagnosis (Figure 5.4). In this age group the mean estimated time to develop drug-resistance from diagnosis was 3.8 years.

Irrespective of age, the risk was highest in patients with generalized cryptogenic/symptomatic epilepsies (Figure 5.5): 15.6% at 1 year, 23.5% at 3 years, and 39.1% at 5 years from diagnosis. In this syndromic category the mean estimated time to develop drug resistance from diagnosis was 3.3 years.

Younger age and having a generalized symptomatic/cryptogenic or undetermined epilepsy showed a significant association with drug resistance, also after adjusting for sex. Compared to the oldest age class, the adjHR for patients <15 years was 13.80 (95%CI 1.76,108.22). Compared to partial idiopathic epilepsies, the adjHR for generalized symptomatic/cryptogenic epilepsies was 8.46 (95%CI 1.08,66.55) and for undetermined epilepsies was 16.13 (95%CI 1.58,164.89).

5.4.2 Long-term prognosis and prognostic patterns

To calculate prognostic patterns, the considered study population included 405 prevalent cases (on January 1 2000) and 342 incident cases (newly diagnoses between January 1 2000 and December 31 2008). The two samples differed according to age and sex and in the proportion of drug resistant individuals, but not with reference to the main syndromic categories (Supplementary Table 5.3). However, when children (patients less than 18 years) and adults (patients 18 years or older) were compared, the two samples differed in a number of variables, except for disease duration (Supplementary Table 5.4).

Six hundred and fifty-seven individuals (88.0%) were followed for at least two years, 540 (72.3%) for at least five years, 365 (49%) for at least 10 years, and 207 (27.7%) for at least

20 years from diagnosis. Details are presented in Table 5.5. In 42.7% of cases epilepsy diagnosis was at less than 15 years old. Partial seizures were the predominant type (61.6%). Partial symptomatic epilepsies were the commonest syndromic category (35.5%), followed by partial cryptogenic epilepsies (22.4%) and idiopathic generalized epilepsies (20.6%).

As of December 31st 2008, 428 people (57%) had been seizure-free for at least 2 years, 110 of them off-treatment. Thirty-one people had died at last follow-up. The cumulative time-dependent probability of starting 2-year remission was 18% at treatment start, 33.5% at two years, 44.7% at five years, 52.4% at ten years, and 67.2% at 20 years (Fig. 5.6.1A). The probability of having started 2-year sustained remission at 20 years was 59.7% (Fig. 5.6.1B). The probability of starting 5-year remission was 14.5% at treatment start and 21.5% at two years, 29.8% at five years, 34.7% at ten years and 50.2% at 20 years (Fig. 5.6.1C). The corresponding probability of 5-year sustained remission at 20 years was 42.6% (Fig. 5.6.1D). Men had a higher probability than women of starting 2-year remission and 2-year sustained remission (Tables 5.6A and 5.6B). Apart from individuals a75+ years at diagnosis, the probability of starting a 2-year remission and 2-year sustained remission increased with the age at diagnosis (Tables 5.6A and 5.6B). People with partial idiopathic epilepsy had the best prognostic outlook, followed by those with idiopathic generalized epilepsies and partial cryptogenic epilepsies (Table 5.6A and 5.6B). Compared to people starting a 2-year remission after treatment with one or two AEDs, those with DRE had a significantly lower chance of entering a 2-year remission and to be in remission at last follow-up (Table 5.6A and 5.6B). The differences were similar for the probability of attaining 5-year remission and sustained remission (see Tables 5.6C and 5.6D). Only epilepsy syndrome and drug resistance were confirmed as independent predictors of 2-year and 5-year remission (ever and sustained) (Table 5.7).

Syndromes and drug-resistance (ILAE definition) were significantly different between those in 2-year and 5-year terminal remission and those not. Partial and generalized idiopathic and

partial cryptogenic epilepsy was more prevalent in the remission group, while generalized symptomatic/cryptogenic epilepsy was more prevalent in those not in remission at last follow-up than in other groups. Sex and age at diagnosis were unremarkable (data not shown).

Thirteen individuals followed for at least five years had incomplete data and were excluded from the prognostic patterns assessment. The 527 remaining had: 1. Early remission: 101 (19%); 2. Late remission: 175 (33%); 3. Remission followed by relapse: 85 (16%); 4. No remission: 166 (31%). Table 5.8 shows the prognostic patterns according to clinical and demographic factors. Only epilepsy syndrome, number of drugs used and response to AEDs significantly determined long-term prognostic patterns. Late remission was more prevalent in generalized idiopathic, partial cryptogenic and idiopathic epilepsy than in other syndromes while in generalized symptomatic/cryptogenic epilepsy or partial symptomatic epilepsy no remission was the predominant pattern. 36.5% of people with generalized symptomatic/cryptogenic epilepsies attained early or late remission. Post-hoc comparisons revealed that partial idiopathic epilepsy was highly represented in late remission (52%, $p=0.0466$) and underrepresented in the group never entering remission (10.5%, $p=0.0267$), while generalized symptomatic/cryptogenic and partial symptomatic epilepsies were strongly represented in the remission never group (48.1%, $p=0.0379$ and 38.5%, $p=0.0229$, respectively).

Almost one fifth (17%) of people taking one AED never attained remission. The percentage increased to 34% in those receiving two different drugs and to 62% in those receiving to three or more drugs. The post-hoc comparisons confirmed that patients taking one AED were rare in early and late remission (29.7%, $p<0.0001$ and 40.2%, $p=0.0009$, respectively) and less present in the group never entering remission (17.1%, $p<0.0001$), while patients taking three or more AEDs were rare in early and late remission (1.9%, $p<0.0001$ and 17.0%, $p=0.0004$, respectively) and most represented in the group never entering remission (62.2%,

p<0.0001). 69.6% of people who failed two or more drugs never entered remission while 18% experienced remission followed by relapse and 11.4% had late remission. In the logistic regression models, the response to treatment was the only variable associated with differing prognostic patterns. In people with drug-resistant epilepsy, the odds ratio (OR) of having early remission was 0.03 (95% CI 0.01 to 0.25). The corresponding OR for late remission was 0.11 (95% CI 0.05 to 0.25) and for remission followed by relapse was 0.39 (95% CI 0.19 to 0.82) (p<0.0001).

5.4.3 AEDs withdrawal

The study sample consist of 747 people with epilepsy aged 11 months through 94 years and followed for a total of 11,045.5 person-years (mean 14.8 years; interquartile range 4.5-22.5). Clinical characteristics are provided in Table 5.5; 731 people (98%) were treated with at least one AED.

The use of each compound as first, second, third, or fourth to ninth AED is shown in Table 5.9. The three AEDs most commonly used as first drug were valproate, carbamazepine and phenobarbital and the same drugs were also the commonest second option. The third option included, in decreasing order, carbamazepine, levetiracetam and topiramate.

The commonest reasons for drug withdrawal were, in decreasing order, terminal remission, ineffectiveness and adverse events. Table 5.10 shows the reasons for withdrawal with reference to the sequence of drug assignment. For the first AED, the main reasons for withdrawal were terminal remission followed by ineffectiveness; for the second AED the main reasons were ineffectiveness followed by terminal remission; for the third and the fourth AED the main reason was ineffectiveness, followed by adverse events. Withdrawal for ineffectiveness increased from the first to the seventh drug, while withdrawal for terminal remission decreased progressively after the first drug. Adverse events showed a moderate increase from the first to the last assigned drugs.

Reasons for drug withdrawal for each AED are provided in Table 5.11. The percentages of withdrawal of carbamazepine, phenobarbital and valproate due to ineffectiveness were in general lower than the percentages reported for other AEDs.

5.4.3.1. Cumulative probabilities and predictors of withdrawal of the first, second and third AED

1. First AED.

The cumulative probability of withdrawal of the first AED for ineffectiveness increases from 2.9% at one year to 12.6% at twenty years (Supplementary Table 5.5). The only predictor was age at diagnosis: compared to those aged less than 15 years, those in the 15-64 year group were less likely to withdraw due to ineffectiveness (HR 0.46, 95% CI 0.28-0.75), while those in the oldest group showed no significant differences (HR 1.26, 95% CI 0.61-2.59). The cumulative probability of withdrawing the first AED for terminal remission increased from 1.0% at one year to 20.0% at twenty years. The variables associated with first AED withdrawal due to seizure freedom were age at diagnosis, sex and epilepsy syndrome. Compared to those aged less than 15 years, those in the 15-64 year group were less likely to withdraw the drug (HR 0.58, 95% CI 0.40-0.86) while those in the oldest group had a similar HR although this was not statistically significant. Females had a lower probability than males of withdrawing the drug (HR 0.56, 95% CI 0.39-0.82). Those with cryptogenic/symptomatic epilepsies (HR 0.43, 95% CI 0.29-0.63) had a lower probability of withdrawing the drug than those with idiopathic epilepsies. The cumulative probability of withdrawing the first drug for adverse events was 0.5% at one year and increased to 3.3% at twenty years. The probability of withdrawing the first drug for other reasons was 0.2% at one year and 6.6% at twenty years. Predictors for adverse events and other reasons were not assessed, due to the small numbers. No significant differences were observed between old and new AEDs given as first treatment (Supplementary Table 5.6). Four hundred and sixty people never withdrew the first antiepileptic treatment and 224 of them (50.9%) started a

period of remission lasting until the end of follow-up. The cumulative probability of either withdrawing the first AED for seizure freedom or of achieving sustained remission while still on treatment was 23.1% at one year and increased to 48.0% at twenty years.

2. Second AED. The cumulative probability of withdrawing the second drug at twenty years for ineffectiveness was 15.8%, for adverse events 4.3%, for terminal remission 13.3%, and for other reasons 7.7% (Supplementary Table 5.5). The only variable associated with discontinuation of the second AED for ineffectiveness was seizure type: compared to partial seizures, generalized seizures were more likely to lead to drug withdrawal (HR 2.05, 95% CI 1.10-3.83). Due to the small number of events, predictors for other reasons for the withdrawal of the second AED were not evaluated. No significant differences were found between old and new AEDs (Supplementary Table 5.6).

3. Third AED. The cumulative probability of withdrawing the third AED at twenty years for ineffectiveness was 39.3%, for adverse events 8.0%, for seizure freedom 4.3%, and for other reasons 5.0% (Supplementary Table 5.5). Due to the small numbers, predictors for the third AED withdrawal were not assessed. The comparison between old and new AEDs showed no significant differences (Supplementary Table 5.6).

5.4.3.2. Cumulative probabilities and predictors of withdrawal of the most commonly used AEDs

At 20 years, the cumulative time-dependent probability of withdrawal of carbamazepine for ineffectiveness was 10.8%. The corresponding values were 13.5% for phenobarbital and 12.3% for valproate (Figure 5.7A). The 20-year probability of withdrawal for terminal remission was 12.9% for carbamazepine, 14.8% for phenobarbital and 27.4% for valproate (Figure 5.7B).

Predictors of withdrawal due to ineffectiveness were seizure type for carbamazepine and age for phenobarbital. No predictors were found for valproate. Generalized seizures were more likely than partial seizures to lead to withdrawal of carbamazepine for ineffectiveness (HR

3.07, 95% CI 1.35-6.98). Individuals in the 15-64 years group had a lower probability of withdrawing phenobarbital due to ineffectiveness than the youngest age group (HR 0.24, 95% CI 0.11-0.54), while those in the oldest group had a similar HR although this was not statistically significant.

Variables associated with drug withdrawal due to seizure freedom were sex for carbamazepine and age, sex and syndrome for valproate. No predictors were found for phenobarbital. Females had a lower probability of withdrawing carbamazepine for seizure freedom than males (HR 0.47, 95% CI 0.22-0.99). Compared to people in the <15 year group, those aged 15-64 years were less likely to withdraw valproate due to ineffectiveness (HR 0.30, 95%CI 0.13- 0.70), while those in the oldest group had a similar HR although this was not statistically significant; females had a lower probability of withdrawing the drug than males (HR 0.52, 95% CI 0.30-0.91); compared with idiopathic epilepsies, those with cryptogenic/symptomatic epilepsies were less likely to have drug withdrawal (HR 0.35, 95% CI 0.19-0.65).

Due to the small number of events, cumulative probabilities and predictors of carbamazepine, valproate and phenobarbital withdrawal for adverse events and other reasons were not assessed.

5.4.4 Tables and Figures

Table 5.1. Prevalence (Pr) of active epilepsy as of December 31 2008

	Prevalence			
Population	**N**	**N prevalent cases**	**Pr*1,000**	**95%CI**
M	71,541	341	4.77	4.26 , 5.27
W	74,965	343	4.58	4.09 , 5.06
Total	146,506	684	4.67	4.32 , 5.02
M				
<15y	15,700	51	3.25	2.36 , 4.14
15-34y	15,361	82	5.34	4.19 , 6.49
35-54y	21,380	104	4.86	3.93 , 5.80
55-74y	14,920	74	4.96	3.83 , 6.09
75+y	4,180	30	7.18	4.62 , 9.74
W				
<15y	15,152	49	3.23	2.33 , 4.14
15-34y	15,214	80	5.26	4.11 , 6.41
35-54y	20,960	103	4.91	3.97 , 5.86
55-74y	15,868	74	4.66	3.60 , 5.72
75+y	7,771	37	4.76	3.23 , 6.29
Total				
<15y	30,852	100	3.24	2.61 , 3.88
15-34y	30,575	162	5.30	4.48 , 6.11
35-54y	42,340	207	4.89	4.22 , 5.55
55-74y	30,788	148	4.81	4.03 , 5.58
75+y	11,951	67	5.61	4.27 , 6.94

Legend: 95%CI = 95% Confidence Interval; M = Men; W = Women; y = Years.

Table 5.2. Prevalence (Pr) of drug resistant epilepsy in the year 2008

	Prevalence			
Population	**N**	**N prevalent cases**	**Pr*1,000**	**95%CI**
M	71,541	39	0.55	0.37 , 0.72
W	74,965	68	0.91	0.69 , 1.12
Total	146,506	107	0.73	0.59 , 0.87
M				
<15y	15,700	10	0.64	0.24 , 1.03
15-34y	15,361	7	0.46	0.12 , 0.79
35-54y	21,380	14	0.65	0.31 , 1.00
55-74y	14,920	6	0.40	0.08 , 0.72
75+y	4,180	2	0.48	0.00 , 1.14
W				
<15y	1,5152	14	0.92	0.44 , 1.41
15-34y	15,214	16	1.05	0.54 , 1.57
35-54y	20,960	23	1.10	0.65 , 1.55
55-74y	15,868	15	0.95	0.47 , 1.42
75+y	7,771	0	0.00	0.00 , 0.00
Total				
<15y	30,852	24	0.78	0.47 , 1.09
15-34y	30,575	23	0.75	0.44 , 1.06
35-54y	42,340	37	0.87	0.59 , 1.16
55-74y	30,788	21	0.68	0.39 , 0.97
75+y	11,951	2	0.17	0.00 , 0.40

Legend:95%CI = 95% Confidence Interval; W = Women; M = Men; y = Years.

Table 5.3. Demographic and clinical characteristics of non drug-resistant and drug resistant epilepsy in the prevalent and incident population (n=684).

		Prevalent population					**Incident population**				
Variable	**Category**	**Total**	**Non-drug-resistant**		**Drug-resistant**		**Total**	**Non-drug-resistant**		**Drug-resistant**	
		N	**N**	**%**	**N**	**%**	N	N	%	N	%
Gender	W	343	275	80.2	68*	19.8	154	135	87.7	19	12.3
	M	341	302	88.6	39	11.4	188	171	91.0	17	9.0
Seizures	Focal	432	365	84.5	67	15.5	218	198	90.8	20	9.2
	Generalized	227	193	85.0	34	15.0	105	92	87.6	13	12.4
	Unclassifiable	25	19	76.0	6	24.0	19	16	84.2	3	15.8
Syndrome	PI	44	43	97.7	1**	2.3	23	22	95.7	1[#]	4.3
	PS	253	209	82.6	44	17.4	133	120	90.2	13	9.8
	PC	157	134	85.4	23	14.6	78	72	92.3	6	7.7
	GI	129	117	90.7	12	9.3	59	56	94.9	3	5.1
	GC/GS	71	51	71.8	20	28.2	33	23	69.7	10	30.3
	Undetermined	24	19	79.2	5	20.8	12	9	75.0	3	25.0
	Special	6	4	66.7	2	33.3	4	4	100.0	0	0.0
Age[§]	<15y	100	76	76.0	24***	24.0	120	97	80.8	23[##]	19.2

	15-34y	162	139	85.8	23	14.2	70	69	98.6	1	1.4
	35-54y	207	170	82.1	37	17.9	62	55	88.7	7	11.3
	55-74y	148	127	85.8	21	14.2	69	65	94.2	4	5.8
	75+y	67	65	97.0	2	3.0	21	20	95.2	1	4.8
Disease duration at the time of diagnosis	<1year	609	512	84.1	97	15.9	302	267	88.4	35	11.6
	≥1year	72	62	86.1	10	13.9	39	38	97.4	1	2.6
	Missing data	3	3	100.0	0	0.0	1	1	100.0	0	0.0

Legend: W = women; M = Men; PI = Partial Idiopathic; PS = Partial Symptomatic; PC = Partial Cryptogenic; GI = Generalized Idiopathic; GC/GS = Generalized Cryptogenic/Generalized Symptomatic; y = Years.

**P*=0.0025 ***P*=0.0019; ****P*=0.0054 (compared to non drug-resistant epilepsy)

[#]*P*=0.0024; [##]*P*=0.00012 (compared to non drug-resistant epilepsy)

[§]In the incident population, age was calculated at diagnosis.

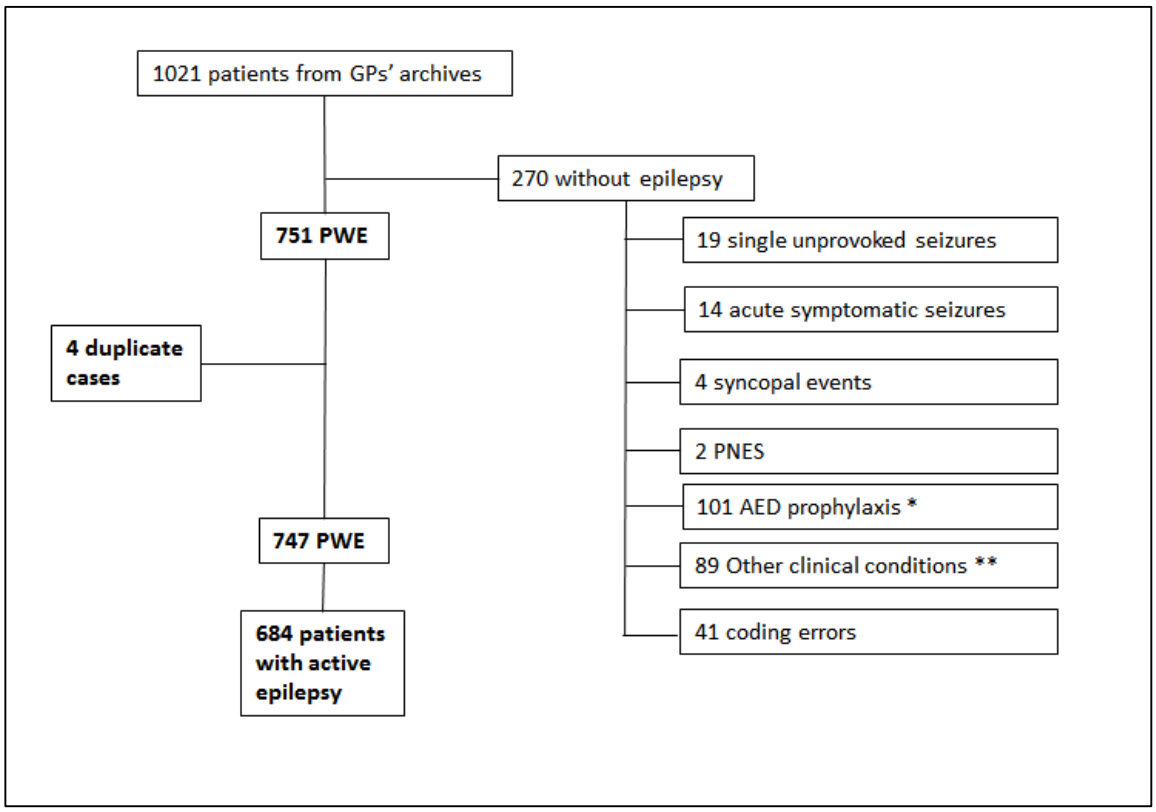
Table 5.4. Factors associated with drug-resistant epilepsy in multivariable logistic regression models.

		Prevalent population			Incident population		
Variable	**Category**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Gender				0.0030			0.3995
	W	2.0	1.3 - 3.2		1.4	0.6 - 3.0	
	M (ref.)	1.0			1.0		
Syndrome				0.0032			0.0280
	PI (ref.)	1.0			1.0		
	PS	20.6	2.7 - 157.3		6.5	0.7 - 56.4	
	PC	16.2	2.1 - 126.8		5.3	0.6 - 50.5	
	GI	7.0	0.9 - 56.3		1.7	0.2 - 18.0	
	GC/GS	21.6	2.7 - 170.9		14.4	1.6 - 128.4	
	Spec.	50.9	3.5 - 734.3		-	-	
	Undet.	25.0	2.6 - 240.0		20.7	1.6 - 269.4	
Age*				<0.0001			0.0039
	<15y	25.2	5.2 - 122.3		7.9	0.9 - 67.6	
	15-34y	8.3	1.8 - 38.4		0.4	0.02 - 7.0	
	35-54y	6.4	1.4 - 28.6		2.9	0.3 - 26.0	
	55-74y	5.1	1.1 - 23.5		1.5	0.5 - 15.0	
	75+y (ref.)	1.0			1.0		
Disease duration							

at the time of diagnosis				0.4030			0.1160
	<1 year (ref.)	1.0			1.0		
	>=1 year	0.7	0.3 - 1.5		0.2	0.02 - 1.1	
Duration of follow-up	1 year increase	1.05	1.02 - 1.06	<0.0001	0.9	0.8-1.1	0.3247

Legend: 95%CI = 95% Confidence Interval; W = Women; M = Men; y = Years; OR = odds ratio; PI = Partial Idiopathic; PS = Partial Symptomatic; PC = Partial Cryptogenic; GI = Generalized Idiopathic; GC/GS = Generalized Cryptogenic/Generalized Symptomatic. *In the incident population, age was calculated at diagnosis.

Figure 5.1. Study flow-chart



Legend: GPs= General practitioners; PWE = Patients with epilepsy; PNES =Psychogenic non-epileptic seizures; AED = Antiepileptic drugs.

*AED prophylaxis in cerebrovascular accidents (49), in brain tumors (31) and in traumatic brain injury (21).

**Other conditions: Psychiatric diseases (50), Migraine/ neuropatic pain (17), Parkinson/dementia (7), Peripheral neuropathies (5), Neonatal hypoxia (4), Hydrocephalus (2), Restless leg syndrome (1), Behçet syndrome (1), Lupus erythematosus (1), Dizziness (1).

Figure 5.2. Cumulative time-dependent probability of drug resistance in incident patients with epilepsy in the overall sample

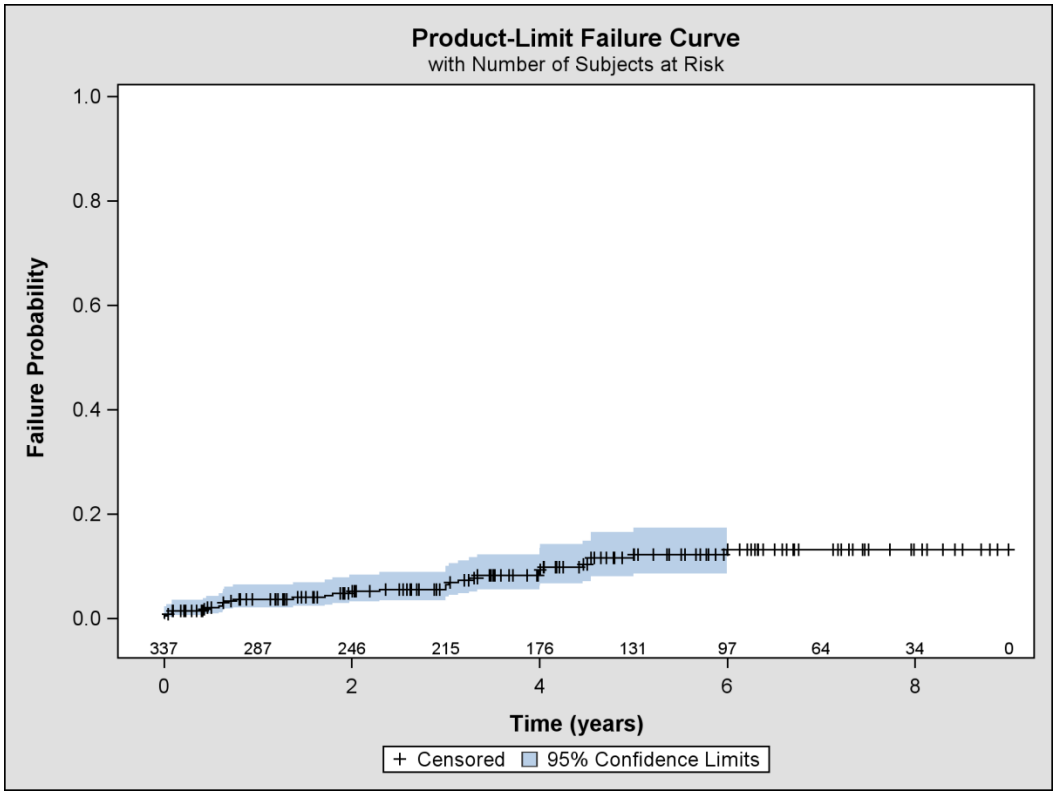


Figure 5.3. Cumulative time-dependent probability of drug resistance in incident patients with epilepsy by sex

Legend: F= female; M = male. The shadows represent the 95% confidence interval.

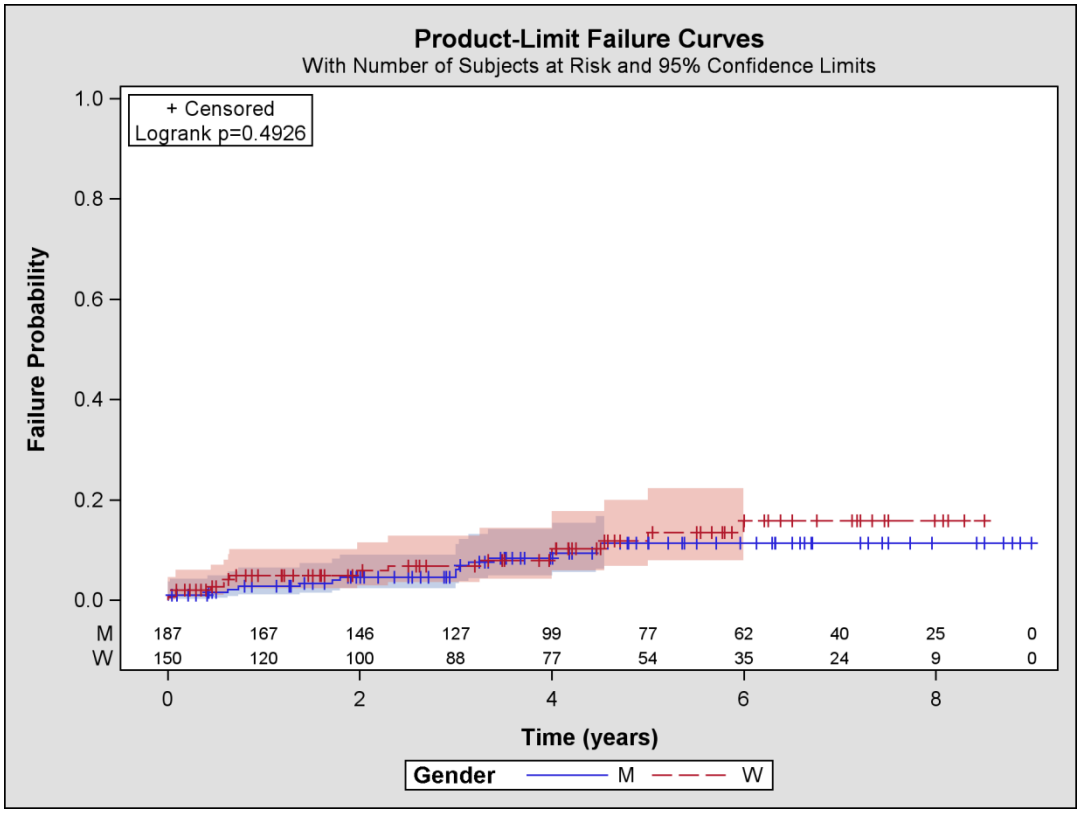


Figure 5.4. Cumulative time-dependent probability of drug resistance in incident patients with epilepsy by age

Legend: The shadows represent the 95% confidence interval.

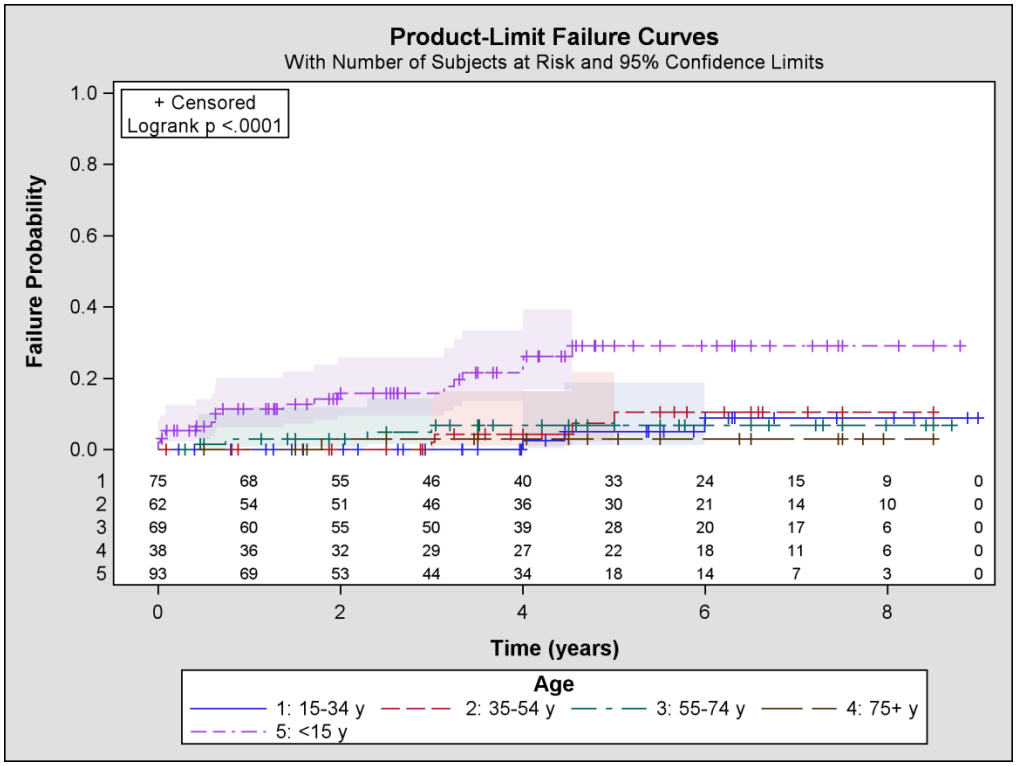
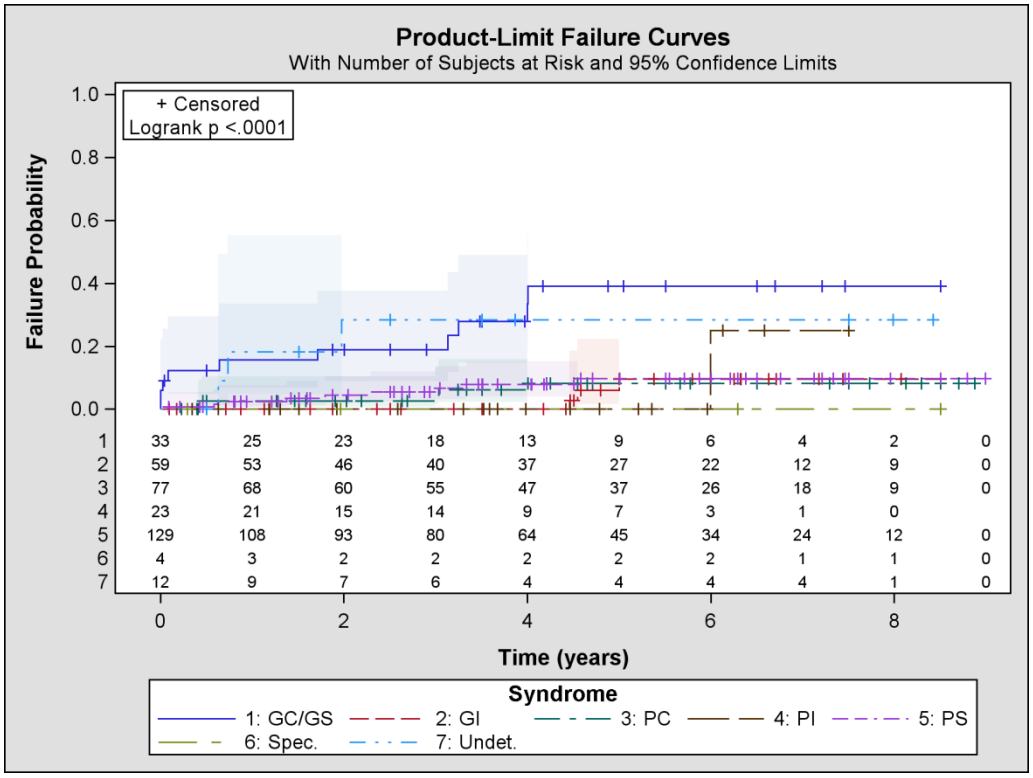


Figure 5.5. Cumulative time-dependent probability of drug resistance in incident patients with epilepsy by syndrome

Legend: The shadows represent the 95% confidence interval.



Legend: PI = Partial Idiopathic; PS = Partial Symptomatic; PC = Partial Cryptogenic; GI = Generalized Idiopathic; GC/GS = Generalized Cryptogenic/Generalized Symptomatic.

Figure 5.6. Cumulative time-dependent probability of attaining 2-year remission (A), 2-year sustained remission (B), 5-year remission (C), and 5-year sustained remission (D) in the study cohort

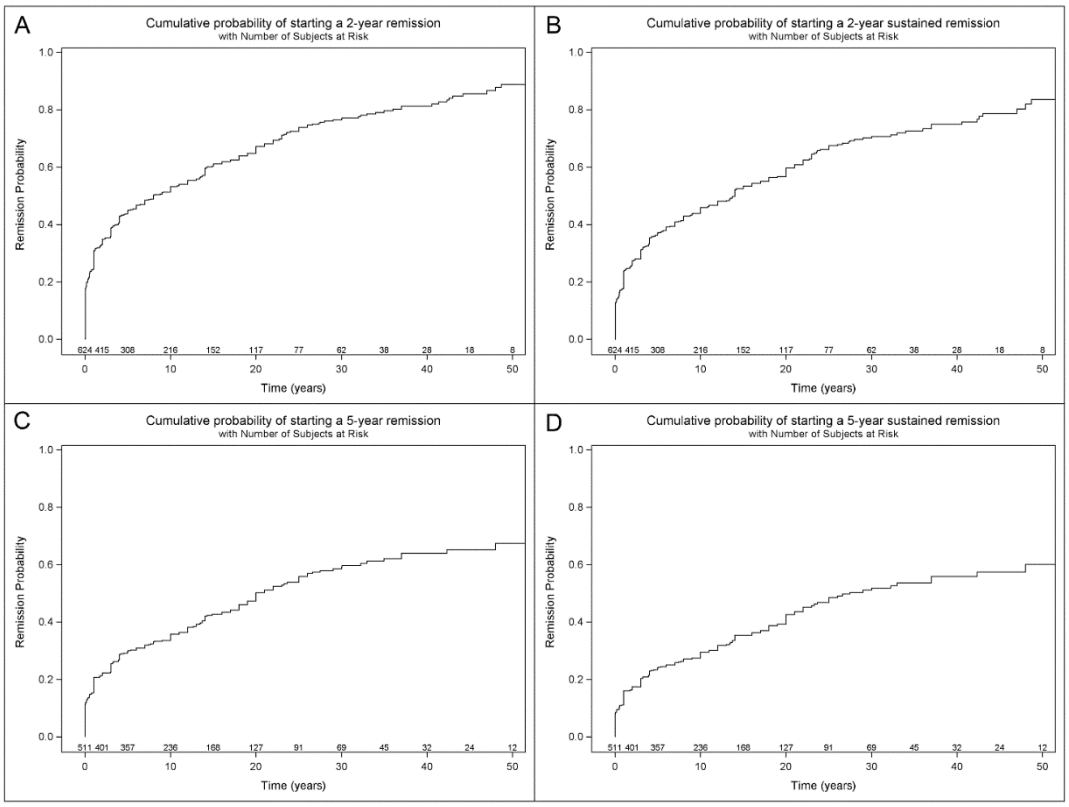


Table 5.5. General characteristics of the sample (n=747)

Variable	Category	N	%
Gender	F	366	49.0
	M	381	51.0
Family history of seizures	Yes	111	14.9
	No	584	78.2
	Unknown	52	6.9
Seizures	Partial	460	61.6
	Generalized	260	34.8
	Unclassifiable	27	3.6
Syndrome	GC/GS	74	9.9
	GI	154	20.6
	PC	167	22.4
	PI	54	7.2
	PS	265	35.5
	Undetermined	26	0.9
	Special	7	3.5
Age at diagnosis	<15y	318	42.7
	15-34y	183	24.6
	35-54y	120	16.1
	55-74y	100	13.4
	75+y	24	3.2
	Missing	2	
Disease duration at diagnosis	<1y	666	89.5
	≥1 y	78	10.5
	Missing	3	
Drug resistant	No	640	85.7
	Yes	107	14.3
Age at diagnosis for broad categories	<15y	318	42.7
	15-64y	353	47.4
	65+y	74	9.9
	Missing	2	
Number of AEDs	0	16	2.1
	1	393	52.6
	2	199	26.6

	3	74	9.9
	4+	65	8.7

Legend: W women; M Men; GC/GS Generalized Cryptogenic/Generalized Symptomatic; GI Generalized Idiopathic; PC Partial Cryptogenic; PI Partial Idiopathic; PS Partial Symptomatic;
y Years; AED Antiepileptic drug.
*Any type of seizures in all known relatives.

Table 5.6. Cumulative time dependent probability of attaining 2-year remission, 2-year sustained remission, 5-year remission, 5-year sustained remission by selected demographic and clinical variables. Univariate analysis

	A. Cumulative probability of starting a 2-year remission						B. Cumulative probability of starting a 2-year sustained remission						C. Cumulative probability of starting a 5-year remission						D. Cumulative probability of starting a 5-year sustained remission					
Years of follow-up	**0**	**2**	**5**	**10**	**20**	**p-value**	**0**	**2**	**5**	**10**	**20**	**p-value**	**0**	**2**	**5**	**10**	**20**	**p-value**	**0**	**2**	**5**	**10**	**20**	**p-value**
Sex						0.0035						0.0202						0.0020						0.0150
M	21.5	37.6	49.9	56.7	72.4		14.6	28.9	41.3	49.2	65.6		14.4	26.1	35.8	39.1	57.4		9.8	19.4	28.0	31.7	49.5	
W	14.0	28.9	39.0	47.7	62.0		10.9	23.1	32.6	40.5	54.1		9.5	16.9	23.7	30.1	43.6		7.5	14.0	20.1	25.0	36.8	
Age at diagnosis						<0.001						<0.001						0.0001						<0.001
<15y	13.3	27.3	36.1	43.3	57.1		9.6	20.4	28.4	35.5	48.0		8.0	15.5	22.1	27.1	41.4		5.3	11.3	17.0	21.1	33.4	
15-34y	20.8	35.2	47.5	54.0	70.8		13.9	25.8	37.8	44.8	62.3		15.0	22.9	32.9	36.9	55.4		10.0	16.9	24.7	28.4	46.0	
35-54y	22.2	36.4	48.2	56.3	79.1		17.2	31.2	43.0	50.5	76.3		15.2	26.6	32.9	40.9	57.6		12.7	23.1	29.8	36.5	54.4	
55-74y	20.8	45.5	60.6	78.6	91.5		16.9	39.2	55.0	75.6	90.2		14.8	35.2	46.5	49.2	77.8		13.0	28.7	41.2	44.1	75.5	

75+y	27.8	44.4	62.5	62.5	-		11.8	32.1	54.2	54.2	-		16.7	25.0	41.7	41.7	-		8.3	17.5	35.8	35.8	-	
Syndrome						<0.0001						0.0001						0.0001						0.0001
GC/GS	6.5	17.7	17.7	32.9	40.9		4.8	11.6	11.6	27.9	33.7		7.7	11.5	11.5	20.3	26.2		5.8	5.8	5.8	15.1	18.2	
GI	21.1	35.3	52.3	59.8	73.9		14.3	24.5	41.3	48.5	65.5		14.2	23.0	37.2	42.5	59.1		9.7	18.2	30.7	34.3	52.1	
PC	19.9	36.9	52.2	60.8	72.8		13.6	29.2	45.5	54.4	65.6		14.2	23.3	31.7	35.8	47.3		10.0	18.0	26.1	29.3	37.7	
PI	23.9	45.7	54.4	66.2	86.4		19.6	39.1	48.8	62.1	83.1		13.9	25.0	41.7	51.2	80.4		11.2	22.7	34.6	45.4	75.6	
PS	15.2	30.9	40.3	44.4	61.6		12.0	26.2	34.7	38.5	55.3		8.3	20.1	25.4	28.2	44.2		7.1	16.3	21.9	24.0	38.9	
Special	40.0	60.0	60.0	60.0	60.0		20.0	46.7	46.7	46.7	46.7		40.0	60.0	60.0	60.0	60.0		20.0	46.7	46.7	46.7	46.7	
Undetermined	30.0	40.0	45.0	50.5	62.9		15.0	27.1	27.1	34.4	42.6		18.8	25.0	31.3	37.5	52.4		6.3	13.5	13.5	21.3	30.1	
Drug resistant						<0.0001						<0.0001						<0.0001						<0.0001
No	20.6	37.6	50.1	58.5	74.9		15.2	30.3	42.7	51.6	68.6		13.7	24.5	34.1	39.8	58.4		10.2	19.7	28.2	33.5	51.6	
Yes	3.2	10.6	14.0	17.9	24.9		0.0	3.4	5.7	8.5	12.6		2.5	5.1	6.3	7.7	11.5		0.0	0.0	1.3	1.3	1.3	

Legend: W = women; M = Men; GC/GS = Generalized Cryptogenic/Generalized Symptomatic; PC = Partial Cryptogenic; PI = Partial Idiopathic; PS = Partial Symptomatic; y = Years.

Table 5.7. Selected demographic and clinical predictors of 2-year and 5-year remission. Multivariate analysis

		2-year remission						5-year remission					
		All			Sustained			All			Sustained		
Variable	**Category**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Gender				0.3160			0.7963			0.1041			0.3859
	F	ref.			ref.			ref.			ref.		
	M	1.11	0.91 - 1.36		1.03	0.82 - 1.29		1.25	0.96 - 1.63		1.14	0.85 - 1.54	
Age at diagnosis				0.6724			0.7587			0.2096			0.3169
	<15y	ref.			ref.			ref.			ref.		
	15-34y	1.20	0.93 - 1.54		1.16	0.87 - 1.55		1.39	0.99 - 1.93		1.32	0.91 - 1.93	
	35-54y	1.04	0.76 - 1.42		1.08	0.77 - 1.53		1.38	0.90 - 2.09		1.48	0.93 - 2.34	
	55-74y	1.18	0.84 - 1.65		1.22	0.85 - 1.75		1.65	1.03 - 2.64		1.64	0.98 - 2.74	
	75+y	1.08	0.57 - 2.05		0.92	0.44 - 1.92		1.35	0.53 - 3.45		1.17	0.41 - 3.35	
Syndrome				<0.0001			<0.0001			0.0002			0.0002
	GC/GS	0.33	0.20 - 0.54		0.27	0.16 - 0.47		0.27	0.14 - 0.51		0.20	0.09 - 0.43	
	GI	0.63	0.44 - 0.92		0.51	0.34 - 0.77		0.58	0.37 - 0.92		0.51	0.31 - 0.84	
	PC	0.58	0.39 - 0.85		0.50	0.33 - 0.76		0.42	0.25 - 0.69		0.35	0.20 - 0.61	
	PI	ref.			ref.			ref.			ref.		
	PS	0.45	0.31 - 0.65		0.38	0.26 - 0.58		0.38	0.24 - 0.60		0.36	0.21 - 0.59	
	Special	0.67	0.21 - 2.21		0.51	0.12 - 2.15		1.10	0.33 - 3.72		0.89	0.20 - 3.87	
	Undetermined	0.68	0.37 - 1.25		0.54	0.26 - 1.09		0.55	0.26 - 1.14		0.39	0.16 - 0.97	
Drug resistant				<0.0001			<0.0001			<0.0001			0.0002
	No	ref.			ref.			ref.			ref.		

Yes	0.28	0.19 - 0.43	0.16	0.09 - 0.28	0.18	0.09 - 0.35	0.02	0.01 - 0.98

Legend: HR = Hazard Ratio; 95%CI = 95% Confidence Interval; F = female; M = Male; GC/GS = Generalized Cryptogenic/Generalized Symptomatic; PC = Partial Cryptogenic; PI = Partial Idiopathic; PS = Partial Symptomatic; y = Years

Table 5.8. Prognostic patterns by selected demographic and clinical variables

		Early remission		Late remission		Remission-relapse		Remission never		
Variable	**Category**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**p-value***
Gender	F	43	16.6	89	34.4	39	15.0	88	34.0	0.3469
	M	58	21.6	86	32.1	46	17.2	78	29.1	
Seizures	Partial	61	19.2	103	32.4	48	15.1	106	33.3	0.5234
	Generalized	38	19.5	68	34.9	32	16.4	57	29.2	
	Unclassifiable	2	14.3	4	28.6	5	35.7	3	21.4	
Syndrome	GC/GS	4	7.7	15	28.8	8	15.4	25	48.1	0.0046
	GI	25	21.0	45	37.8	22	18.5	27	22.7	
	PC	27	22.1	38	31.2	20	16.4	37	30.3	
	PI	9	23.7	20	52.6	5	13.2	4	10.5	
	PS	32	18.4	52	29.9	23	13.2	67	38.5	
	Special	2	40.0	0	0.0	1	20.0	2	40.0	
	Undetermined	2	11.8	5	29.4	6	35.3	4	23.5	
Age at diagnosis	<15y	35	14.9	75	31.9	41	17.5	84	35.7	0.3039
	15-34y	26	18.4	50	35.5	26	18.4	39	27.7	
	35-54y	21	25.9	27	33.3	8	9.9	25	30.9	
	55-74y	16	28.1	20	35.1	7	12.3	14	24.5	
	75+y	3	23.1	3	23.1	3	23.1	4	30.7	

	Missing									
Disease duration	<1y	88	18.6	161	34.0	73	15.4	152	32.1	0.2914
at diagnosis	≥1 y	13	24.5	14	26.4	12	22.6	14	26.4	
Number of AED	0	0	0.0	0	0.0	1[§]	20.0	4[^]	80.0	<0.0001
	1	80	29.7	108	40.2	35	13.0	46	17.1	
	2	19	12.9	49	33.3	29	19.7	50	34.0	
	3+	2	1.9	18	17.0	20	18.9	66	62.2	
Drug resistant	No	100	22.3	166	37.0	71	15.9	111	24.8	<0.0001
	Yes	1	1.3	9	11.4	14	17.7	55	69.6	

Legend: W = women; M = Men; GC/GS = Generalized Cryptogenic/Generalized Symptomatic; GI = Generalized Idiopathic; PC = Partial Cryptogenic; PI = Partial Idiopathic; PS = Partial Symptomatic; y = Years; AED = antiepileptic drugs.

* Univariable chi-square; ^ 1 patient, age 15, with GI epilepsy; 2 patients, age 88 and 74, taking only diazepam at the time of the seizures; 1 patient, age 83, with brain tumor; § 1 patient, age 31, with GI epilepsy.

Table 5.9. Administration frequency of first, second and third drug by active principle

	First drug		Second drug		Third drug		Fourth to ninth drug
	N	**%**	**N**	**%**	**N**	**%**	**N**
BSC	18	2.5	7	2.1	1	0.7	1
CBZ	203	27.8	60	17.8	18	12.9	4
CLB	2	0.3	22	6.5	12	8.6	7
CNP	2	0.3	31	9.2	8	5.8	16
ESM	9	1.2	4	1.2	4	2.9	2
GBP	2	0.3	6	1.8	4	2.9	6
LEV	13	1.8	32	9.5	18	12.9	29
LTG	4	0.5	32	9.5	13	9.4	15
OXC	31	4.2	16	4.7	5	3.6	10
PB	197	26.9	39	11.5	9	6.5	3
PHT	27	3.7	20	5.9	1	0.7	1
PGB	1	0.1	3	0.9	6	4.3	4
PRM	0	0.0	3	0.9	8	5.8	3
TGB	1	0.1	0	0.0	0	0.0	2
TPM	4	0.5	13	3.8	14	10.1	10
VGB	3	0.4	4	1.2	5	3.6	2
VPA	211	28.9	44	13.0	12	8.6	7
VPM	3	0.4	2	0.6	1	0.7	1
ZNS	0	0.0	0	0.0	0	0.0	3
Total N patients*	731		338		139		65
Old AEDs	672	91.9	232	68.6	74	53.2	45
New AEDs	59	8.1	106	31.4	65	46.8	81

AED Antiepileptic drugs, BSC Barbexaclone, CBZ Carbamazepine, CLB Clobazam, CNP Clonazepam, ESM Ethosuximide, GBP Gabapentin, LEV Levetiracetam, LTG Lamotrigine, OXC Oxcarbazepine, PB Phenobarbital, PHT Phenytoin, PGB Pregabalin, PRM Primidone,
TGB Tiagabine, TPM Topiramate, VGB Vigabatrin, VPA Valproate, VPM Valpromide, ZNS Zonisamide.
*16 did not start drugs.

Table 5.10. Reasons of drug withdrawal by order

Ranking	Patients treated	Ineffectiveness		Adverse events		Terminal remission		Other*		Never withdrawn	
	N	N	%	N	%	N	%	N	%	N	%
First	731**	83	11.3	20	2.7	117	16.0	45	6.2	460	62.9
Second	338**	45	13.3	11	3.2	24	7.1	20	5.9	232	68.6
Third	139	33	23.7	6	4.3	4	2.9	6	4.3	90	64.7
Fourth	65	22	33.8	3	4.6	0	0.0	2	3.1	38	58.5
Fifth	31	11	35.5	2	6.5	2	6.5	0	0.0	16	51.6
Sixth	18	6	33.3	0	0.0	1	5.6	0	0.0	11	61.1
Seventh	7	3	42.9	0	0.0	0	0.0	0	0.0	4	57.1
Eighth	3	0	0.0	2	66.7	0	0.0	0	0.0	1	33.3
Ninth	2	0	0.0	1	50.0	0	0.0	0	0.0	1	50.0

*Death, drug out of production, pregnancy, own volition.
** Missing information about AED withdrawal in six.

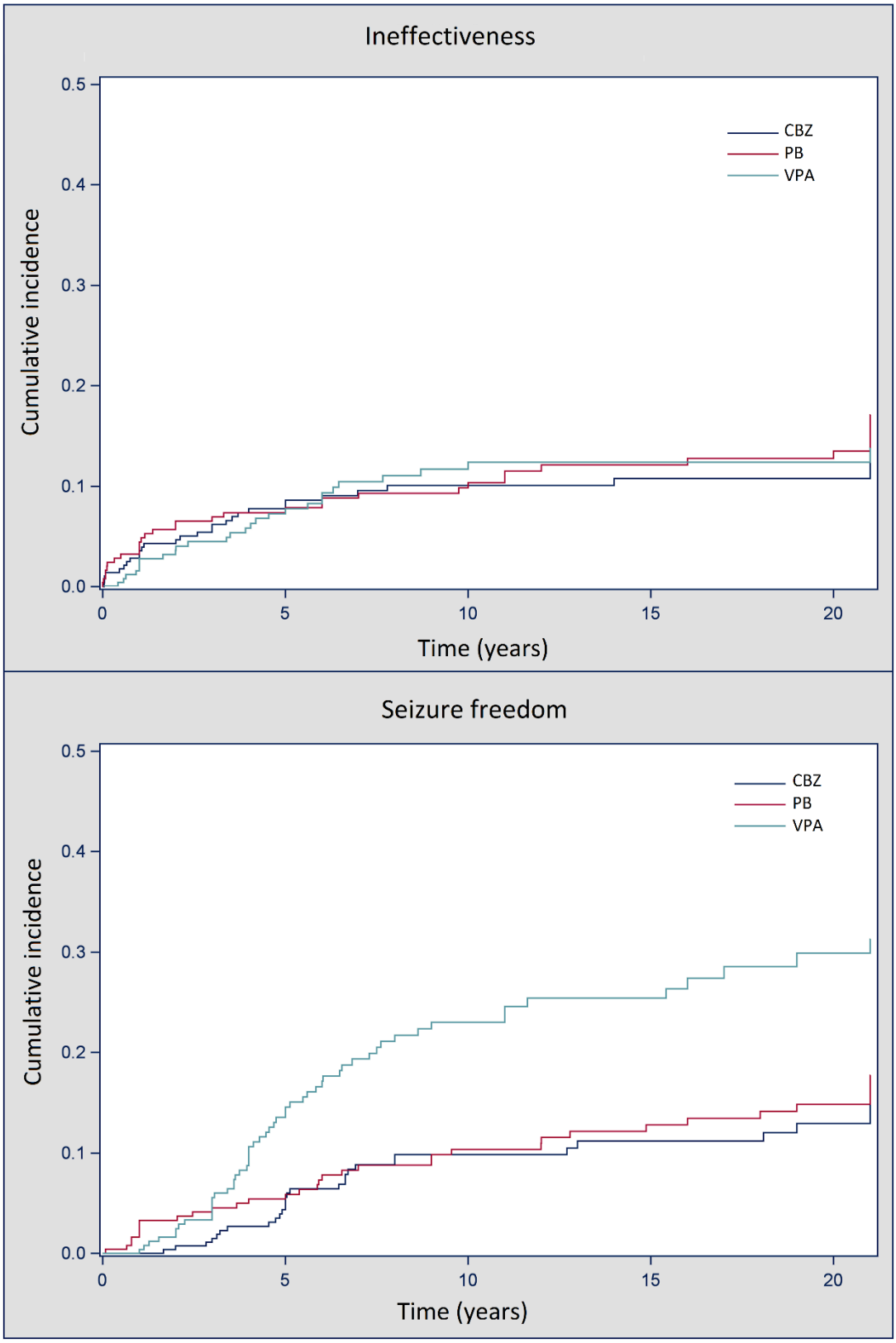
Table 5.11. Frequency of reasons of drug withdrawal by active principle

	Patients treated	Ineffectiveness		Adverse events		Terminal remission		Other*		Never withdrawn	
	N	N	%	N	%	N	%	N	%	N	%
BSC	27	6	22.2	1	3.7	4	14.8	9	33.3	7	25.9
CBZ	285	31	10.9	16	5.6	29	10.2	15	5.3	194	68.1
CLB	43	12	27.9	0	0.0	2	4.7	2	4.7	27	62.8
CNP	57	6	10.5	1	1.8	1	1.8	2	3.5	47	82.5
ESM	19	4	21.1	0	0.0	6	31.6	0	0.0	9	47.4
GBP	18	12	66.7	0	0.0	0	0.0	0	0.0	6	33.3
LEV	92	12	13.0	5	5.4	3	3.3	0	0.0	72	78.3
LTG	64	15	23.4	1	1.6	2	3.1	4	6.3	42	65.6
OXC	62	10	16.1	3	4.8	5	8.1	3	4.8	41	66.1
PB	248	34	13.7	7	2.8	34	13.7	23	9.3	150	60.5
PHT	49	16	32.7	3	6.1	2	4.1	4	8.2	24	49.0
PGB	14	1	7.1	0	0.0	0	0.0	2	14.3	11	78.6
PRM	14	2	14.3	0	0.0	1	7.1	1	7.1	10	71.4
TGB	3	2	66.7	1	33.3	0	0.0	0	0.0	0	0.0
TPM	41	11	26.8	4	9.8	4	9.8	1	2.4	21	51.2
VGB	14	7	50.0	0	0.0	2	14.3	0	0.0	5	35.7
VPA	274	27	9.9	3	1.1	55	20.1	8	2.9	181	66.1
VPM	7	0	0.0	0	0.0	1	14.3	1	14.3	5	71.4
ZNS	3	0	0.0	0	0.0	0	0.0	0	0.0	3	100.0
Old AEDs	1023	138	13.5	31	3.0	135	13.2	66	6.5	654	63.9
New AEDs	311	70	22.2	14	4.5	16	5.1	10	3.2	201	64.6

AED Antiepileptic drug, BSC Barbexaclone, CBZ Carbamazepine, CLB Clobazam, CNP Clonazepam, ESM Ethosuximide, GBP Gabapentin, LEV Levetiracetam, LTG Lamotrigine, OXC Oxcarbazepine, PB Phenobarbital, PHT Phenytoine, PRG Pregabalin, PRM Primidone, TGB Tiagabine, TPM Topiramate, VGB Vigabatrin, VPA Valproate, VPM Valpromide, ZNS Zonisamide.

* Death, drug out of production, pregnancy, own volition withdrawal.

Figure 1. Cumulative incidence functions for withdrawal of carbamazepine, phenobarbital and valproate, for ineffectiveness (A) and terminal remission (B).



6. DISCUSSION

Epilepsy is a chronic neurological disorder with heterogeneous phenotype. The heterogeneity of the disease has several diagnostic and therapeutic implications. A relevant diagnostic implication is represented by the common misdiagnosis of PNES as epilepsy with consequent negative reflections for the response to the available antiepileptic drugs. The frequency of DRE is perhaps inflated by a number of patients who have PNES without genuine epileptic seizures. The exclusion of these patients may not only lead to a more correct management of the disease but it also helps defining the true burden of DRE. Unfortunately, in the absence of VEM, the differential diagnosis can only rest on the contribution of history, clinical signs and, if available, video recording of the seizure(s). Based on our findings, videos themselves help making a correct diagnosis of PNES characterized by motor signs. In about one third of cases a confident diagnosis of PNES/ES can be established by trained epileptologists on clinical ground based on video data alone and our results benefit all affected patients, particularly those with no access to VEM units.

In all the patients with PNES, we found a number of variables to differentiate PNES from ES. Investigating the patients themselves and their witnesses using ad-hoc structured questionnaires, some variables have been identified with high SE and SP, some of them also reaching statistically significance. These instruments may be useful clinical tools applicable in settings not offering the facilities for a correct diagnosis and in cases where the gold standard has failed.

When psychiatrists have been included in the study, they demonstrated to be less accurate than neurologists in diagnosing PNES but were more attuned to capture the subtleties of human behaviour, or subjective experiences as the effects of hidden internal conflicts, and they contributed a new lexicon in defining PNES. The different elements valued by

neurologists and psychiatrists imply the need to have joint consultations to refine the diagnosis.

In the study on the characterization of idic(15) syndrome, epilepsy was used as disease tracer. It was found to be one of the few symptoms on which satisfactory agreement was found. regarding its presence or absence. Unfortunately, epilepsy was present in similar proportions in the idic(15) and in the syndromes characterized by intellectual disability and abnormal behaviour. Epilepsy is thus a reliable diagnosis but is not a marker of this genetic syndrome. Other focused studies are needed to further investigate this issue.

To verify if the epilepsy phenotype is static or dynamic and can be affected by the response to the available drugs, a population based-study in a well-defined area of Italy was performed. Our data indicate that 1/6 patients with active epilepsy in the general population has DRE and 1/10 patients with newly diagnosed epilepsy will develop DRE within nine years from the diagnosis.

Furthermore, the long-term prognosis of epilepsy is favorable in most cases. However, early seizure remission is not invariably followed by terminal remission and seizure outcome varies according to well-defined patterns. Also drug-resistant patients can reach terminal remission. This is a demonstration of the dynamic phenotype of epilepsy and, most importantly, DRE.

Prolonged seizure remission and prognostic patterns can be predicted by broad syndromic categories and the failure of two antiepileptic drugs. We also observed that the AED given at diagnosis is retained in the majority of cases. Seizure freedom, lack of efficacy and adverse effects were, in decreasing order, the commonest reasons for AED discontinuation. Withdrawal can be predicted by age at diagnosis, sex, disease characteristics and varies among drugs.

In the following subsections I report an extended and focused discussion for each research project.

6.1 MI-RO PNES Study

6.1.1 Discussion about the prediction of the diagnosis of PNES versus ES

This study offered an opportunity to define how experts in the field of epilepsy utilize visual clues to establish the diagnosis of epilepsy versus non-epilepsy. Raters' attention was focused on the presence of elementary signs typically associated with ES or PNES, and at the same time on how these signs are linked and develop, either in a progressive evolution that follows the CNS organization or in a disorganized manner, incongrous with neurological pathophysiology. This conforms to the pre-learned model of ES and PNES that includes a number of positive signs associated with, or exclusive of, the diagnosis of either diagnosis. It also explains why in the raters' comments the term "semiology" was the most frequently mentioned as key to the diagnosis. This approach was most likely successful in cases with ES or PNES but almost always failed when the diagnosis was Other NES. There are two possible explanations for this observation: 1) motor manifestations, that we found directly correlated with the ability to match the GS diagnosis, are more likely to be represented in ES and PNES than in Other NES; 2) for the diagnosis of Other NES, additional information about the prodromal symptoms and the results of monitoring other physiological parameters (EKG telemetry, blood pressure, etc.) is necessary. Raters were quite aware of these limitations and chose in many such cases to withhold a diagnosis (Cannot Say) stating: "diagnosis impossible" or "cannot be reached with confidence based on video alone".

An important factor affecting raters' accuracy was the number of diagnostic clues detected. The presence of multiple signs and objective symptoms increased accuracy because objective signs are more reliable than subjective reports and the joint occurrence of various signs increases specificity, as reported by others (Sayed et al, 2011).

Our study, investigating the reliability of video data alone, duplicates the results of a previous study (Benbadis et al, 2009). Interrater variability in interpreting videotaped events was present in about equal measure, whether the EEG was included or excluded. Kappa values in the two studies for the overall group and for each diagnostic category were very close. Interrater agreement in predicting the GS diagnosis was comparable. This finding was corroborated by the additional observation that in our study, among the three "best" raters, the two (R-1 and R-4), both blind to the patients' history and EEG findings, performed just as well as R-5 who was not blind. This suggests that, in some cases, the video provides key information so typical that knowledge of the simultaneous EEG has little impact on diagnostic accuracy.

Our findings underscore the position of the ILAE Task Force (LaFrance et al, 2013) that in the majority of cases a correct diagnosis is based on the convergence of (1) history, (2) witnessed semiology, (3) monitoring of multiple physiological functions (EEG, EKG, other autonomic). At the same time, our data indicate that not in all cases the three elements are essential to reach the diagnosis, confirming the observation that not infrequently epileptologists are quick in differentiating ES from PNES on video before viewing the EEG. Since it is proven that the ability to discriminate one type of seizure from another is a learned skill and requires neurological training (Ristić et al, 2015; Seneviratne et al 2014; MacDonalds et al, 2012) one note of caution is that reviewers must be properly trained and experienced. One major cause of concern is the variable degree of competence among reviewers and how it affects inter-rater agreement.

Our 5 raters, interpreting video data alone, were not exempt from such liability. Two raters performed consistently at a lower level of accuracy compared to the other three. That may be explained, at least for one who was a child neurologist, by lower exposure during clinical practice to the adult population that was the focus of this investigation. However the diagnosis based on video alone showed concordance among all five raters and was correct

in almost one third of the videos reviewed. In this study motor seizure semiology diagnoses fared better than non-motor seizures, confirming the results of a previous study (King et al, 1982). As reported by others (Seneviratne et al, 2012), some seizure types were easier than others to diagnose based on videos. In our sample these seizures were represented by focal seizures with secondary generalization and complex and rhythmic motor PNES. The reasons for that are in the raters comments, indicating that video alone was not useful, was inadequate and at times misleading in the case of non-motor, sensory and dyscognitive seizures**.**

A correct prediction of the putative diagnosis also depends on video quality. Videos recorded in hospital rooms during VEM, are not constantly supervised and capture spontaneous events that often go unnoticed or are only partially witnessed by staff. Indeed, missing relevant features such as the proper display of the subject and subject's behaviour, a dysfunctional audio or lack of intervention by bystanders, were the most common reasons for the video rated below the minimum desirable standard. However, after removing poor quality videos from analysis, interrater agreement improved only slightly. This can be explained by the differing reasons given by the raters to qualify a video as inadequate, some of which unlikely to affect the diagnosis, and by the non-unanimous quality assessment among raters. Nonetheless, efforts to improve video quality would be valuable. For example, the use of a video made through a mobile device can have a higher quality and the caregiver could be trained to frame the face or body movements and to record the audio. The problem could be the missing of the seizure start, but not in the case in which prodromal symptoms are present, because a family member could be alerted and start to record the video. It is a problem for an epileptic seizure (focal or generalized).

The main strenghts of this investigation are the prospective approach, the inclusion of all eligible candidates consecutively admitted for monitoring, and a collection of data prior to the diagnosis. This provided a cohort of patients with mixed seizure disorders reflecting the current referral pattern to epilepsy monitoring units and allowed to investigate these subjects

without bias, contrary to many previous PNES studies based on retrospective data. Our main contribution is a closer insight on how epileptologists utilize the information, displayed on video of events recorded during hospital monitoring. Such approach has however inhertent constraints. For instance, while some events such as rhythmic motor PNES are possible to diagnose on video alone, others such as sensory, non-motor or autonomic events, are not.

This study presents some limitations. First, the number of cases investigated in this feasibility study is small. Second**,** our restricted cohort did not include "hypermotor PNES", a rather uncommon type that is notoriously difficult to differentiate from hypermotor frontal lobe seizures. Third, patients with other NES diagnosis were only four and no patients with a double diagnosis of ES + PNES were enrolled. Fourth, patients were enrolled only in a single epilepsy unit. Patients seen in other tertiary referral centers/ epilepsy units' may be different. In addition, we cannot exclude that subjects with other-socio-cultural background present with different phenotype. In order to solve this questions, we need a large prospective international comparing different populations. Fifth, the number and background of our raters is fairly small and selected, which may have affected the results.

On the other hand, our results were worthwhile for a number of reasons. First, they provide useful information for the power analysis of larger studies. Second, they generate new hypotheses and stimulate new research. Third, our experience proves that international collaboration is possible in compliance with privacy regulations, and exchange of personal information such as video images through the Internet is acceptable. This is an opportunity for exploring patient populations where manifestations and frequency of PNES may vary in relation to cultural differences (Asadi-Pooya and Sperling, 2015). Most importantly, it may spur new interest in the video format, once defined as "the closest proxy to witnessed events" (MacDonald et al, 2012). A greater use of this modality may be particularly beneficial when VEM is not available. This is relevant not only for future research but also for clinical

purposes. The utilization of homemade videos as a method of screening patients before admission to a full monitoring unit and its diagnostic value could be further explored. Finally, because clinical assessment based on video alone can easely lead to misdiagnosis, further investigations are needed to identify clinical parameters necessary to corroborate a video diagnosis in settings where full VEM investigation is not accessible.

6.1.2 Discussion about the prediction of the diagnosis of PNES versus ES engaging psychiatrists.

By most statistical measures, experienced epileptologists were more skilful than a group of practicing psychiatrists in blindly predicting the GS diagnosis, based exclusively on the physical semiology of a "seizure". This result was expected considering that, contrary to epileptologists, psychiatrists seldom have the opportunity to directly scrutinize events on video. However, whereas degree of interrater agreement within groups was quite different, success rate in the two groups was almost comparable when the opinions of individual raters examining each single video were compared. The comments presented to justify the diagnosis of choice may explain this apparent contradiction. They indicate that psychiatrists, encouraged by training, during the unfolding of an event, detect subtle psycho-dynamic indicators that can be utilized as diagnostic tools in addition to pure semiology**.** Such signs or manifestations are implicitly part of the currently accepted definition of PNES but can be easily ignored by professionals with less psychodynamic experience.

According to the ILAE recommendations (LaFrance et al, 2013), the diagnosis of PNES is essentially based on the following criteria: inconsistent semiology with clinical manifestations that do not conform to a coherent neurological scheme as ES do; lack of the required neuro-physiological substrate (ictal EEG discharges); evidence of risk factors that may lead to the "episodic impairment of self-control" as defined by Reuber (Reuber, 2008). The ILAE definition, like the DSM III definition, fails to unravel the underlying mechanisms

of PNES also described as "experiential or behavioural responses to emotional or social distress" (LaFrance et al, 2013). The experiment reported here was an attempt to determine how different and complementary would be the observations of fully boarded psychiatrists compared to those of experienced epileptologists. The results have been somewhat perplexing but encouraging. Despite limited training and unfamiliarity with the type of video material submitted, the individual psychiatrists in our panel, blind to patient's history and EEG findings, were very close to experienced epileptologists in predicting the GS diagnosis. However, they were clearly inferior and in greater disagreement with each other when challenged as a group. It is possible that such discrepancy in interrater agreement as a group and as individual pairs (high for epileptologists, low for psychiatrists) reflects the different approach in the interpretation of the video material adopted by the two groups. Epileptologists, by training, tend to strictly adhere to pre-set criteria based on semiological features validated in published material. Such disciplined approach confers considerable uniformity to the raters as individuals and as a groups. Conversely, psychiatrists, though paying due attention to the same indicators, are not exclusively bound to evidence-based criteria, displaying greater sensitivity to nuances and to the significance of subtle behavioural features. Table 6 shows examples of how psychiatrists read into body language and interpret subtle behavioural manifestations or subjective experiences as the effects of hidden internal conflicts. This willingness to explore beyond the mere facts and to capture cryptic signals otherwise ignored in a more orthodox approach, probably explains the success of the psychiatric raters in predicting the correct diagnosis when considering a single case.

There are no data in the literature that prove the validity and reliability of this approach. Our preliminary data indicate that out of 14 videos where at least one of the raters included psychodynamic observations in his comments to justify the diagnostic choice, the diagnosis was correct in 9 (7 PNES; 2 ES) and incorrect in the remaining 5 videos (4 ES and 1 NDP).

This suggests that psychiatrists are more successful in diagnosing PNES than other types of seizures.

Though the sample was small, it clearly indicates that the psychodynamic interpretation of certain behavioural signs can be helpful in diagnosing PNES but can also be misleading, especially in differentiating non-motor PNES from complex focal seizures. Other explanations can be given to interpret the different findings when comparing the diagnostic attitudes of psychiatrists and neurologists. Psychiatrists lost the habit of diagnosing PNES, as patients with this clinical condition directly go to the neurologist, who makes the first differential diagnosis. On the other hand, the neurologist deals with the "physical" body, that corresponds to the “homunculus” (sensory and / or motor) in the CNS, while the psychiatrists deal with the symbolic body (Focault, 2006), that corresponds to the representative language of an original trauma and whose semiology does not correspond to any “homunculus” of the CNS. The expertise that the psychiatrist put in the field, in addition to the epileptologist, consists in reading the symbolic body language, as previously observed in the "indifference", in the "partially in touch with the context / hesitating as if wanting to gain time”, or in "putting herself at the center of attention".

Indeed, psychiatrists seem to have poor skills in non-PNES and non-ES attacks, where symbolic body language is virtually absent, while they add elements to the diagnosis of PNES, where the symbolic body language is present (Cornaggia et al, 2017, submitted). Conversely, epileptologists seem to have good skills in motor ES, where topodiagnosis appears more straightforward and simple, while they appear to have less skill in seizures where the relationship between seizure semiology and “homunculus” is less obvious. For this kind of seizures, a simple video documentation seems unsatisfactory, whether made by the epileptologist or by the psychiatrist, because of the intricate overlap between the somatic and the symbolic body. In these instances, VEM or linguistic analysis assume an essential role.

It is well known from the epilepsy literature that, so far, no single indicator has proved pathognomonic for the diagnosis of either ES or PNES. Rather, a constellation of signs or symptoms may be more indicative (Sayed et al, 2011). It appears that assessing the diagnostic weight of any single feature mentioned by the psychiatrists may be equally problematic. Our results indicate that certain observations can be misleading even for experienced psychiatrists. Signs must be interpreted carefully, in context, and gain significance if supported by additional evidence. In this respect, the convergence of multidisciplinary observations made by epileptologists in collaboration with psychiatrists should be ideal.

In recent years, psychiatrists have been deterred from directly participating in the diagnostic process of identifying PNES by several factors. First, the replacement in the DSM III of the term "hysteria" with a phenomenological classification of symptoms and manifestations devoid from etiological content. That, in itself, has curbed their interest in the condition. Second, the realization that diagnosing PNES has become, by default, a responsibility of the epileptologists who, by necessity, work with physical evidence and physiological parameters. Third, there is a widespread trend in medicine of relying primarily on evidence-based data and downplaying the importance of intuitive contributions. As a result, we have been paying great attention to external manifestation and less to what the patient has to express or communicate subliminally. A first sign of renewed interest in the hidden signals contained in patients' behaviour has been a series of publications on the differences in linguistic expression between subjects with ES compared to PNES (Cornaggia et al, 2012; Reuber et al, 2009; Schwabe et al, 2007).

This experiment was undertaken to explore the observations psychiatrists had to offer. We decided to challenge them with material ostensibly more suitable for epileptologists for the sake of comparing the two groups. More trials will be necessary using more appropriate material such as recorded patient's interviews, rather than, or in addition to, the events

recorded on video. Though only tentative, some of the observations reported here should make us reflect on the opportunities we are missing. Psychiatrists, by training, are more attuned to capture the subtleties of human behaviour than neurologists and can contribute a new lexicon in defining PNES. Thus, they can play an important complementary role not only in establishing the diagnosis but also, by offering a glimpse onto the possible pathophysiological mechanisms of this disorder, paving the way to effective treatment. Thus, the issue is with pursuing further by continuing the dialogue and fostering more active collaboration between epileptologists and psychiatrists in the management of patients with PNES.

This study has limitations. First, the number of raters who took part in the study is fairly small. This, in itself, can affect the results. Second, we tried to involve individuals with varying degree of seniority and diverse knowledge and experience about seizure disorders, who were representative of practicing psychiatrists. Nonetheless, the participating psychiatrists may not reflect the background and experience of all psychiatrists in clinical practice in Italy and, perhaps even more important, in other countries. Most importantly, our finding that individual psychiatrists may be as accurate as individual epileptologists even without specific training must be interpreted with caution, keeping in mind that the level of expertise of the single participating raters is crutial. Clearly, the addition of one poor rater, or of one excellent rater, to either side could substantially change the accuracy ratio between the two groups. However, our results, though far from definite, provide insight in a fairly unexplored field and can be used as the background to stimulate new research.

6.1.3 Discussion about the use of a new questionnaire for differentiating PNES from ES.

The use of questionnaires to discern PNES from ES is not new. Devices used so far have varied greatly in format and size, depending on the intended purpose and targeted population. In general, their content has focused on the somatic manifestations of the events, (Rugg-Gunnet al., 2001; Rosemergy et al., 2013; Sen et al., 2007), or on specific features (eyes forcefully closed / changes in amplitude and rhythm of body movements) (Sadan et al., 2016). Other characteristics like history of chronic fatigue and fibromyalgia (Benbadis 2005) and the frequency of panic symtpoms in patients with PNES and epilepsy (Hendrickson et al, 2014) and also in other non epileptic events (syncope) (Rawlings et al, 2017) should be considered in future instruments to distinguish PNES from other diagnosis. An abbreviated version of review of systems questionnaires has recently proved useful in differentiating PNES from ES (Asadi-Pooya AA et al., 2016), including only ten questions about ten different systems and asking for presence/absence of abnormalities. Relatively little attention has been given to the personality characteristics and emotional dysregulation that constitute an important component in the pathogenesis of PNES (Reuber M et al., 2004). Only more recently, and in a few, isolated instances, investigators have inquired about emotional states and subjective experiences such as anxiety and depersonalization, asking patients and witnesses to fill ad-hoc questionnaires, the Paroxysmal Event Profile (PEP) for patients and the Paroxysmal Event Observer (PEO) for witnesses. (Reuber M et al., 2011). The PEP questionnaire was also used in a more recent study to explore the diagnostic potential of this instrument in patients with PNES and transient loss of consciousness (TLOC) (Reuber et al, 2016). In another study, patients were asked to describe their symptoms freely and through structured interviews (revised version of the Psychosensory-Psychomotor Phenomena Interview) (Sharrack S and Garlovsky J, 2015). Other investigators have tailored instruments for specific purposes such as a rapid screening of patients presenting with seizures in the Emergency Department (DePaola et al., 2016) or extensive questionnaires for self-reporting. However, the methodology of this last study

(Syed et al., 2009) was quite selective, excluding eyewitness and "sensitive" questions (i.e. history of abuse) because responses could be unreliable. Moreover, it did not include in the analysis the large contingent of PNES characterized by pure subjective or minimal manifestations because, in the absence of EEG abnormalities, they were undistinguishable from simple focal seizures. Thus, the study missed potential sources of valuable information. Different results are reported about the engagement of witnesses. In some prospective studies, they were not able to indentify clinical sign useful to epileptologists after in-person or telephone interview (Syed et al, 2008, Syed et al 2011). But in another retrospective study that involves seizure witnesses using a 34-item questionnaire, they turned out to be more aware of seizure triggers and a relationship between PNES and emotional stress than patients (Reuber et al, 2011). Clinicians have totake note of the different sources of information during the diagnostic process (Reuber et al, 2011).

Overall, lack of standardization, differences in methodology and the perception that results are often conflicting, have generated among professional uneasiness and skepticism about the use of questionnaires as clinical tools. Such attitude is justified by the belief that a face-to-face interview, especially if combined with VEM, is the best approach. Since this remains the undisputed gold standard, so far screening questionnaires have been recommended primarily as a way to accelerate, rather than reduce, referrals to epilepsy centers. For this reason, we devised an eclectic, easy to manage instrument that could be incorporated in the assessment of patients presenting with seizures, as review of system questionnaires have become routine part of medical consultations. Our questionnaires were empirically based on a mix of data reported in the literature as diagnostic predictors and anecdotal clinical observations that, in our judgment, could help differentiating PNES from ES. We included all types of seizures without exception but asked each subject to specify which types, if they had more than one. We asked all questions deemed pertinent, including those that could cause embarrassment and retained two separate questionnaires because in clinical practice,

especially in the absence of VEM, clinicians must rely on both patients' and eyewitnesses reports. Finally, since the aim of our study was to identify a tool helpful in the differential diagnosis, we chose as best predictors the SE and SP of each variable against the final diagnosis.

Our results, in accordance with previous reports, indicate that structured questionnaires can help differentiating PNES from ES though the number of diagnostic predictors is limited. Quantitatively, this study identified only 7 variables above the pre-set *discriminating threshold* for Questionnaire A and 2 for Questionnaire B.

Qualitatively, some of the predictive variables emerged from Questionnaire A (direct patient's response) distinctly call attention to the state of anxiety and emotional turmoil fostering the events. They consist of prominent subjective manifestations of anxiety (headache, heart racing, tingling and numbness) that probably correspond to the changes in cardiac system activity preceding and following PNES recently described (Reinsberger et al., 2012). Contrary to the systematic search for the aura when suspecting ES, this is an area that is scarcely investigated when suspecting PNES. Likewise, the other predictive variables highlight the recurring themes of hypersensitivity to pain (pre-ictal headache / post-ictal pain) and tendency toward somatization (history of chronic fatigue), all common in patients with PNES. Surprisingly, among the history of abuse, only physical abuse, frequent in PNES and rare in ES, reached the discriminating threshold (SE =58.8/ SP 81.8). By resetting the discriminatory threshold to a lower value of SE and SP, we identified additional variables retaining some degree of diagnostic value (Table 3.3.2). They include; two triggering factors: sensitivity to lights and feeling overwhelmed, probably reflecting vulnerability to suggestion and weak coping ability; one post-ictal manifestation: trouble speaking (SE 64.71 / SP 63.64); history of emotional abuse (SE 52.94 / SP 63.64), frequently reported in both syndromes and only slightly more common in PNES. History of self-inflicted injury ("hurt yourself") were predominantly present in PNES and absent in ES. Surprisingly, sexual abuse

(SE 29.41 / SP 81.82), seldom reported and, when present, reported about equally in either syndrome, was relegated among the non-discriminatory variables (see Table e-1).

Conversely, the contribution of Questionnaire B (report by witnesses) was restricted to two discriminating variables. They both highlight the critical role of ictal eye closure and side-to-side head movements in differentiating ES from PNES. In our sample, the presence of these easily recognizable features was highly indicative of PNES and virtually excluded the diagnosis of ES (SE 66.7/ SP100). The differential diagnosis with hypermotor seizures of frontal lobe epilepsy, presenting similar semiology, is relatively simple because, by rule, they occur primarily during sleep. Reversibly, the absence of these key features was consistent with ES though did not exclude PNES. Of note, both variables were present in the majority of patients with PNES and absent in all subjects with ES who responded to these questions, suggesting that the presence of these signs is not compatible with, and thus may exclude, the diagnosis of epilepsy.

One of the 4 variables below threshold emerged from Questionnaire B (Table 4) (ictal movements "on/off") is also distinctive for being predominantly absent in ES. (SE 50.00 / SP 90). This suggests that while eyewitnesses may find difficult to identify such feature when it occurs during PNES, they may find it easier to say when it does not occur. Overall, it appears that sub threshold variables have a complementary role and, therefore, should not be automatically excluded. Furthermore, such observations imply that not only the presence of a sign may be suggestive of a diagnosis but also its absence can be relevant.

Among the advantages of questionnaires are the low cost, the easy administration, the wide spectrum of issues that can be systematically explored and the completeness of the feedback, always with a clear indication of whether a sign is present or absent. The original contributions of our study include first, the confirmation that both patients and eyewitnesses can provide unique and different information and, therefore, are best approached with two separate instruments. Second, the concept that questionnaires focused primarily on typical

signs of the event's semiology may be helpful to specialized professionals but have little impact on patients who, as a rule, are unaware during the events. Likewise, questionnaires are bound to be rather unproductive when addressing eyewitnesses, notoriously unfit to appreciate many of the classic "trade mark" signs identified by epileptologists (Azar et al., 2010; Syed et al., 2011; Rugg-Gunn et al., 2001; Heo et al., 2008). Nonetheless, while eyewitness contributions are limited to the few, concrete observations made during events seen in the past and depend on later recall, patients can provide a wealth of details about their subjective experiences and symptoms before and after the events. This part of seizure semiology may go unnoticed to the eye of a reviewer during VEM but can be easily identified by directly asking the patient through the questionnaire.

There are several limitations to be considered in our study. The small number of eligible patients could have affected the SE and SP of single variables. The analysis of questionnaire B was based on a dataset of only 16 cases (6 PNES, 10 ES), and undermine the validity of any conclusion drawn. Furthermore, the results reflect the comparison between only PNES and ES diagnosis, the only two groups numerically adequate for analysis. Patients with dual diagnosis of PNES + ES (1 case) and patients with other diagnoses unrelated to epilepsy or PNES (for example syncope) (4 cases) had to be excluded. Though the content of our questionnaires seemed broad and comprehensive for screening purposes, the selection of items to be investigated was empirical and based on the clinical judgment of the authors. Thus, we suspect it was neither exhaustive nor complete. We found particularly difficult documenting history of somatization and midway we felt compelled to revise questionnaire A and remove from this domain a few questions deemed inadequate. Despite the high number of missing data, a positive history of chronic fatigue turned out to be among the discriminatory signs for PNES. This indicates that somatization is an important component of this disorder and should be explored systematically, perhaps with the aid of review of system questionnaires. Another source of perplexity is the reliability of self-reported

information. We presume responders are unbiased and trustworthy, even when confronted with sensitive issues in their personal history. However, other investigators have felt differently and for good reasons (Syed et al., 2009).

In conclusion, a larger sample will be needed to confirm the predictors emerged from this study and to determine whether more borderline variables reach the significance threshold.

It is foreseeable that a standardized questionnaire for universal use will be trimmed down to the essential information lay people, patients and eyewitnesses, can provide easily rather than being geared to the criteria utilized by professionals.

Self-reporting questionnaires, though will never reach the degree of certainty provided by VEM, may offer a probability score, based on the presence or absence of relevant variables and their SE/SP values, that may lead to a tentative diagnosis with measurable degree of reliability.

6.2 Discussion about the characterization study of the diagnosis of idic(15) syndrome

The primary objective of the study was the identification of symptoms, signs and instrumental findings, singly or in various combinations comparing patients with idic(15) syndrome to patients with other neurodevelopmental disorders considered in the differential diagnosis. The research question to be addressed was that idic(15) syndrome differs from other neurodevelopmental disorders in a number of symptoms and/or signs whose combination defines a peculiar clinical phenotype. Another important aim was to verify the detection of specific symptoms (including seizures and epilepsy) by different experts in a homogeneous and objective way.

Clinical charts with history of the disease, videos of neurological examinations and instrumental examination of 32 patients were examined by 5 independent raters in order to find a cluster of signs and symptoms able to discriminate the idicdisease from other diseases having similar characteristics.

Cases and controls were enrolled by child neurologist in two participating centers and matched for age and sex. The two groups were no different with reference to standard values of WHO (who.int/childgrowth/en) for gestational age, birth weight, length at birth, head circumference and Apgar score.

Battaglia (Battaglia, 2008) reported that the main clinical characteristics of idic(15) syndrome in more than 75% of cases are: hypotonia, developemental delay/intellectual disability, autistic behaviour, epilepsy, minor dysmorphic features mainly involving face. In 25%-50% of patients brain abnormalities, genitourinary tract defects and growth retardation are expected. In less than 25% of patients congenital heart diseases and microcephaly could be find.

The results obtained in this study indicate that variables easily recognized in patients by raters with a good agreement (>0.6 calculated with Kendall's coefficient W) where almost the same of those described by Battaglia (2008), but high scores of SE and SP were found only for hypotonia and feeding difficulties in the newborn period. When considering this two variables as present in the same patients, SP increased and SE decreased. These results may have a significant value for physicians when assessing a new patient in their clinical practice. These two variables, when combined, help to discriminate idic(15) syndrome from other neurodevelopemental disorders.. A number of cases presenting hypotonia and feeding difficulties in the newborn period could be identified with high accuracy in a population with disability. In particular, 76% of patients with these signs have the disease and 64% of patients without this signs cannot be diagnosed with idic(15) syndrome.

Another problem is that some signs/symptoms could be predictive of the diagnosis but are not uniformly recognized by physicians and for this reason may not lead to the proper diagnosis if the patient is examined by different investigators.

Analysing the results reported in the three steps by the raters, step 1 and 2 made a greater contribution to the correct diagnosis than step 3 (instrumental tests examination). EEG, MRI

and CT-Scan deviated raters from a correct differential diagnosis. Probably because the characteristics of idic(15) syndrome are less diagnostic and recognizable through instrumental examinations but more identifiable investigating the history and performing general and neurological examinations.

The limitation of this study was the limited sample size. The proportion of cases/controls in this sample is rather artifactual but it reflects a setting in which the caring physician is knowledgeable of idic(15) syndrome as a possible diagnosis. The raters were selected among specialists with expertise in the field of rare diseases associated with intellectual disability and epilepsy. The external validity of our results is thus limited.

Future aim is to empower the sample in order to have a larger and more heterogeneous population and to verify if some signs/symptoms could be more predictive of the diagnosis. The study design used here could serve as a model for the clinical assessment of rare neurodevelopmental disorders in the field of disability, in clinical practice and in the research setting.

6.3 The EPIRES Study

6.3.1 Discussion about the results of prevalence of active epilepsy and DRE in a well defined population of Norther Italy

The prevalence of active epilepsy and DRE (conforming to the ILAE definition) (Kwan et al, 2010) in the district of Lecco, a well-defined area of Northern Italy, was determined. The proportion of patients with DRE among incident cases was also calculated.

The prevalence of active epilepsy in the local population was 4.67 per 1,000, which falls within the range of rates (2.3-15.9 per 1,000) previously found in high-income countries (Bell et al, 2014). The rates were fairly similar in men and women until age 54 years, while beyond that age the disease peaked in older men, in keeping with other reports (Olafsson and Hauser, 1999; Rocca et al, 2001). Our data on the prevalence of epilepsy in the older age

classes are comparable with previous reports (Olafsson and Hauser, 1999; Wiebe et al, 1999; Luengo et al, 2001; Oun et al, 2003; Al Rajeh et al, 2001).

According to our data the prevalence of DRE at the end of the study period was 0.73 per 1,000 of the local population. Patients with DRE were 15.6% of the population with active epilepsy. The percentage of DRE found by Sillanpää & Schmidt (Sillanpää & Schmidt, 2006), and by Berg et al. (Berg et al, 2012) (both in a pediatric population), as well as by Picot et al. (Picot et al, 2008) (in a population over 15 years of age) ranged from 15.6 to 22.5%, overlapping our results. By contrast, cohort studies conducted in referral centers (Kong et al, 2014; Brodie et al, 2012; Schiller, 2009) reported higher percentage of DRE (21.5-25.3%), possibly because patients with mild varieties of the disease were not seen in those centers.

In the age group <15 years, we found that the percentage of DRE was 20%, which is in accordance with other community-based studies in pediatric populations (Sillanpää & Schmidt, 2006; Berg et al, 2012). Mohanraj and Brodie (Mohanraje and Brodie, 2006) also found uncontrolled epilepsy less common in the elderly compared to adolescents and adults. These authors also stated that old patients are more likely to have a more favorable outcome than the remaining epilepsy population. Our data seem to be in support of that assumption.

Comparing patients with DRE to those with drug-responsive epilepsy, significant differences were found for sex, syndrome and age in prevalent cases, but no differences between men and women in the incident population. The predominance of DRE in women with prevalent epilepsy is difficult to explain and cannot be due to treatment changes for the use of safer medications. Six women stopped medications for fear of teratogenicity. These cases were not counted as drug failures. Generalized symptomatic or cryptogenic epilepsies and partial symptomatic epilepsies were the commonest syndromes among DRE patients both in the prevalent and incident population. These results are in keeping with most literature reports (Kong et al, 2014; Sillanpää & Schmidt, 2006; Picot et al, 2008; Brodie et

al, 2012; Schiller, 2009). In our sample, patients with DRE were younger than drug-responsive patients: the age groups most represented were <15 years and 35-54 years, whereas the least represented was 75+ years. Our data partly overlap those of Kong et al. (Kong et al, 2014) who found the highest frequency of DRE in the 40-49 year group and the lowest frequency in the 60-69 year group. The peak of DRE in the youngest age groups reflects the predominance of more severe epilepsy syndromes in younger individuals. Undetermined epilepsies were also at high risk for drug resistance. This is not an unexpected finding. In a large Italian population with refractory epilepsy, undetermined epilepsies accounted for 16.8% of pediatric cases (Alexandre et al, 2010). In these cases, the failure of two or more drugs may not be uncommon leading to diagnosis of DRE mainly because of inappropriate use of AEDs.

The cumulative risk to become drug-resistant is time-dependent and varies in relation to age and syndromes. Our findings are in keeping with other reports using the same definition of DRE (Berg et al, 2006; Geerst et al, 2012). Differences are partly explained by the source population, the age and the duration of follow-up. However, in these studies there was an increasing risk of failure of two drugs with time, that finds confirmation in our study. In addition, their finding that the risk of DRE is highest among children with catastrophic epilepsies compares well with our data indicating that patients with generalized symptomatic or cryptogenic epilepsies are more prone to develop drug resistance.

The main strength (and the originality) of this study is the population-base approach. Another strength is the fairly large sample of patients collected over a 9-year screening period. The first limitation is the use of a definition of DRE only partially conforming to the ILAE definition, that specifies that "the seizure-free period should be less than three times the pre-intervention inter-seizure interval or 12 months, whichever is longer" (Kwan et al, 2010). Because the frequency of seizures before treatment was unavailable in our cases, we were unable to assess the duration of seizure-free periods by application of the "rule of

three". Because of the retrospective nature of the study, there are several limitations: the data collection: in the absence of a predefined modality to collect the necessary information, the identification of patients with DRE has been sometimes difficult; it was not possible to determine with certainty whether the diagnosis of epilepsy established by the neurologist consulted on the case was correct; DRE might be underestimated in light of our definition and the limited follow-up; an underascertainment of DRE in elderly individuals cannot be excluded because some of them were not in the direct control of the GPs'; we have been unable to collect follow-up information on patients who left the province during the study period; the nine-year period of the study ended in 2008. However, our findings are not outdated because the frequency and treatment of epilepsy has been virtually unchanged in the last few years. Finally, the small numbers found in some age and sex categories may have a strong influence on the precision of our estimates.

According to the results of this study, 1/6 patients with active epilepsy in the general population have DRE and about 1/10 patients with newly diagnosed epilepsy will develop DRE within nine years from the diagnosis. However, drug resistance is a dynamic process covering several years, which may present a different course in men and women, children and adults, and in different epileptic syndromes. In this regard, the ILAE definition has limitations when used for epidemiological purposes because in clinical practice the medical decisions (including the assessment of treatment failure) cannot be standardized. In addition, as drug resistance is a function of time, its frequency depends on the characteristics of the cohort at risk (whether incident or prevalent) and the duration of the follow-up. The assessment of the prevalence of DRE is meaningless unless it is calculated within a well-defined period of time and, even in this context, it does not take into account the possibility of drug failures outside the study period.

This scenario adds to the complexity of the long-term prognosis of epilepsy, a topic discussed in the following paragraph.

6.3.2. Discussion about the long-term prognosis of epilepsy, prognostic patterns and drug resistance in a well defined population of Northern Italy

Using the recent ILAE definition of DRE and the same prognostic patterns we found that at 20 years 67% of people with epilepsy had attained a 2-year remission of seizures and 50% a 5-year remission. 60% of patients with 2-year remission and 43% of patients with 5-year remission had sustained remission. Seventeen percent of people with at least 2 years of follow-up were off treatment at last observation. This is in keeping with other reports. In a prospective study of 144 people with epilepsy of childhood onset in Finland (selected from a cohort of 245 children), followed for an average of 37 years (Sillanpää & Schmidt, 2006), 48% of people were in 5-year terminal remission (early remission, 16%; late remission, 32%). The UK National General Practice Study of Epilepsy included 729 people of all ages from 275 general practices, followed for a median of 7.1 years (Cockerell et al, 1997). Seventy-one percent entered 5-year remission and 54% were in terminal remission. Remission rates higher than ours have also been reported. In a retrospective study of people with newly diagnosed epilepsy in Rochester, Minnesota, and followed for at least 5 years (Annegers et al, 1979) 76% attained 5-year remission at 20 years and 50% were off-drugs at last follow-up. That was an incident cohort while ours was a prevalent cohort that, by definition, may have missed people with childhood-onset epilepsy who entered remission outside the study period. Our lower probability of 2-year and 5-year remission can be also explained by the shorter period of follow-up after diagnosis. In an extended follow-up of a retrospective cohort of people with epilepsy seen in a UK population of 6,000 from a single general practice (the Tonbridge study) (n=122 in 1983 and n=126 in year 1993), 74% of individuals achieved 4-year remission at 10 years (Cockerell et al, 1995). That study included individuals with at least one non-febrile convulsion and this implies the inclusion

of people with single unprovoked seizures, who have a lower risk of relapse (Hauser et al, 1998; Hesdorffer et al, 2009).

Seizure remission rates tended to increase with age at diagnosis (apart from the oldest age group). Other studies in childhood-onset epilepsy provided 5-year remission rates higher than ours (Berg et al, 2015; Wakamoto et al, 2000; Geerts et al, 2012). The role of age in predicting the long-term outcome of seizures is contradictory (Annegers et al, 1979; Hart et al, 1990) and in our study, although those with onset of seizures below age 15 years had the lowest chance of experiencing seizure remission, conversely to some genetic generalized epilepsy of infancy (Rolandic epilepsy) associated with higher rates of remission, a trend was not confirmed.

People with generalized symptomatic/cryptogenic epilepsies and those with partial symptomatic or cryptogenic epilepsies had lower remission rates than those with other epilepsy syndromes, in line with expectations. Remission can also occur in these syndromic categories, as previously reported (Sillanpää & Schmidt, 2006; Berg et al, 2015; Geerts et al, 2010). These findings support the concept that the long-term prognosis of epilepsy in people with epileptic encephalopathies is not invariably poor in the general population.

About one fifth of our individuals entered early remission, one third entered late remission, one sixth had remission followed by relapse, and one third never entered remission. These findings cannot be compared with other reports as the definitions of the patterns differ. In the Tonbridge study (Cockerell et al, 1995), 49% of people with seizures only at the early stage entered terminal remission (“burst” pattern, to some extent comparable with our early and late remission), 12% had remission periods followed by relapses (“intermittent” pattern, partly overlapping our remission followed by relapse pattern) and 21% had no remission (“continuous” pattern, not dissimilar from ours who never remitted). The differences can be explained by the shorter follow-up in the Tonbridge study; some people with a “burst” pattern might have later relapsed and enterd the “intermittent” pattern. Remission followed

by relapse was observed in 6% of people in the Rochester, Minnesota cohort (Annegers et al, 1979). A more detailed definition of prognostic patterns has been used in a study that followed 516 children with epilepsy for 10+ years. That study identified eight patterns ranging from early 1-year remission, no relapse and complete remission at last follow-up (33%) to never achieving 1-year remission (5%) (Berg et al, 2015). The shorter period of remission (1-year vs. 2-year in our study) may explain in part the higher rates of individuals with early remission and the lower rates of people never achieving remission.

The classification of an individual as drug resistant according to the ILAE definition was compatible with a 30% chance of early or late remission after treatment failure. These findings are in keeping with population-based studies done in children and adults followed for prolonged periods of time (Neligan et al, 2011; Brodie et al, 2012; Geerts et al 2012; Berg et al, 2009) and confirm the concept that the failure of two AEDs is still compatible with subsequent prolonged seizure remission. Our findings are in line with a report on a cohort of adults with chronic refractory epilepsy with long-term follow-up in an epilepsy clinic (Neligan et al, 2012).

The only variable predicting the prognostic pattern was the response to AEDs and, more specifically, drug resistance (ILAE definition). Prognostic patterns can be anticipated by the response to the first treatments rather than the inclusion of an individual in a broad syndromic category.

Strengths and limitations of the EPIRES study have been discussed in the previous paragraph.

The long-term prognosis of epilepsy in a community-based cohort is favourable in about one-half of cases. Seizure remission is followed by discontinuation of treatment in one sixth. Early seizure remission does not, however, invariably lead to terminal remission. Seizure outcome varies according to specific patterns and prolonged seizure remission and prognostic patterns can be predicted only by the response to the first two AEDs. The poor

response to two appropriate AEDs is, however, still compatible with the possibility of entering prolonged remission and even achieving terminal remission, stressing the dynamic nature of drug-resistance.

6.3.3. Discussion about antiepileptic drugs discontinuation by people with epilepsy in a well defined population of Northern Italy

People in our cohort have used a large number of AEDs over a 15-year period. However, during this time, the three most common drugs given at the start of treatment were valproate, carbamazepine and phenobarbital and only 10 percent of people started treatment with a new AED. Terminal remission was the commonest explanation for discontinuation of the first drug (20% at twenty years), followed by lack of efficacy (12.6%). Withdrawal of the first drug for adverse events was only 0.5% at one year and increased to 3.3% at twenty years. While the discontinuation of a drug for terminal remission tended to decrease with AED order, treatment stop for ineffectiveness and for adverse events tended to increase even though clear trends could not be detected because of the small samples at the highest rankings. The reasons for drug withdrawal varied with age, sex and disease characteristics.

The probability of retaining the first drug in the treatment schedule and starting a period of remission lasting until the end of follow-up, or of stopping the first treatment for terminal remission, was high, 48% at 20 years. Others found that the proportion of seizure-free individuals on the first AED ranged from 5.4% to 62% (Kwan and Brodie, 2001; Brodie et al 2012; Lhatoo et al, 2001; Dluglos et al, 2001; Wirrel et al, 2001; Zhang et al, 2013); 63% of our patients never withdrew the first AED and 51% of them started a period of remission lasting until the end of follow-up. This finding supports the concept that in clinical practice the majority of people with epilepsy can be easily controlled with any of the available compounds, appropriately chosen among the available drugs for different epilepsies, even after long follow-up periods.

In our study, the cumulative probability of discontinuing the first drug at 12 months for lack of efficacy or adverse events was only 3.4%. Our findings are fairly similar to the results of a Lebanese study of people with newly diagnosed focal epilepsy, which found a 12-month retention rate of 93.6% (Beydoun et al, 2015). Our data only partly agree, however, with other long-term follow-up studies. In the UK National General Practice Study of Epilepsy (Lhatoo et al, 2001) the first assigned drug was discontinued for lack of efficacy in 21% of cases (compared to our 12.6%) but the discontinuation rate for adverse events was 11.5% (compared to 3.3% in our study). This difference may be explained by the use of carbamazepine, phenytoin, valproate or phenobarbital in 96% of the UK cases as compared to 87% in our cohort. The use of fairly low daily doses for some drugs in our study (see Supplementary Table 5.7) could be another explanation. No differences were found in retention rates when comparing old and new AEDs. Our findings are in keeping with a study in children (Bourgeois et al, 2015) but differ from a study in older adults (Arif et al, 2010) in which the 12-month retention rates ranged from 12.5% (oxcarbazepine) to 90% (valproate). In this latter study, however, the rates were calculated in people with refractory epilepsy.

When comparing drugs in our study, differences in retention were seen. Discontinuation for lack of efficacy was most common with GABAergic drugs while discontinuation for adverse events was mostly seen with topiramate, phenytoin, carbamazepine and levetiracetam in decreasing order. These findings are not unexpected even though the rates differ from those of other reports (Chung et al, 2007; Peltola et al, 2009; Boostma et al, 2009; Kuba et al, 2010; Lhatoo et al, 2000; Hufnagel et al, 2011) on account of differing prescribing patterns and different populations at risk.

People in our cohort taking carbamazepine, valproate or phenobarbital discontinued the assigned treatment for adverse events in 5.6, 1.1 and 2.8% of cases respectively. Our rates are significantly lower than those reported by others (carbamazepine, valproate and

lamotrigine stopped in 27, 13 and 10% of cases respectively) (Kwan and Brodie, 2001). Possible explanations for this difference are the source population and the data acquisition, as our study is a retrospective population-based study and the Scottish study was not, and the use of different daily doses.

Children and elderly subjects tended to stop the first drug mostly for lack of efficacy and, less frequently, due to terminal remission. Childhood and adolescent syndromes less responsive to the current treatments and the need to resort to complex therapeutic regimens in people with comorbidities are possible explanations.

The lower rates of treatment withdrawal due to terminal remission in women than in men likely reflects the higher proportion of females in the age class <15 years (59% versus 41% of male children) who continued the first treatment, perhaps because of the fear of withdrawal in a period of hormonal and emotional changes. As expected, people with idiopathic epilepsies and/or generalized seizures were most likely to respond to the assigned treatments.

As described in the previous sections of this project, because of the retrospective nature of the study, the limitations concern the data collection, in particular it was not possible to determine with certainty whether the diagnosis of epilepsy established by the neurologist consulted on the case was correct; the study period ended in 2008; small numbers of patients have been found in some age and sex categories and this could have influenced our results; data about etiology were not sufficiently detailed.

As limitation of this study, we do not know whether a drug was discontinued after having been given at the highest tolerated dose. Our aim, however, was to explore treatment changes as performed in clinical practice, where the selected daily dose generally represents a compromise between seizure control, adverse events, and individual preference. Another limitation is the time frame during which we started the follow-up. To include people with newly diagnosed epilepsy in the cohort with reasonable follow-up, we started the observation

at a time in which mainly older AEDs were available. We are thus uncertain whether our findings apply to cohorts starting treatment with a new AED. In keeping with our findings, however, there is no evidence from more recent reports (Wilby et al, 2005; Marson et al, 2007; Lee et al, 2014; Weijenberg et al, 2010; Tomson, 2004; Perucca, 2002; Rowan et al, 2005; Steinhoff et al 2003) that new AEDs have advantages over older compounds. Thus, we do not expect significant differences in other therapeutic contexts. Furthermore, the cumulative time-dependent probability of withdrawal of AEDs other than carbamazepine, phenobarbital and valproate was not assessed because of small numbers. The limited sample size can also explain some non-significant correlations between demographic and clinical variables and drug withdrawal. Lastly, we did our best to verify whether the indication for each drug was appropriate. However, we cannot entirely exclude that drug failure was due to incorrect use of a given drug in a given individual.

In conclusion, the majority of people with epilepsy living in a community and followed for a prolonged period of time remain treated with the first assigned drug. Seizure remission is the main reason for drug discontinuation, followed by lack of efficacy and adverse events. Withdrawal of the first drug for ineffectiveness and for adverse events tends to increase by AED order, while decreasing for terminal remission. Withdrawal of the first AED for ineffectiveness can be predicted by age at diagnosis while withdrawal of the second drug is predicted by seizure type, and reflects the predominance of more severe epilepsy syndromes in younger individuals. These findings can help the practicing physician to predict the response to the assigned treatment at diagnosis and when a treatment change is required.

6.4 Description of my involvement and roles in each project

To explain better my personal efforts on every study presented and discussed before, I report here a summary table:

Project Name	**MI-RO PNES**	**Idic(15)**	**EPIRES**
Protocol design		X	X
Start-up procedures	X [a]	X	X
Study coordination	X [a]	X	X
CRF design and production	X	X	X
Data collection	X	X	X
Data management	X	X	X
Data analysis	X [b]	X [b]	X [b]
Results interpretation and discussion	X	X	X
Papers preparation and publication	X	(To be prepared)	X

[a] Only for the Italian group
[b] With the biostatistician

As here reported, my involvement was not only practical (sturt-up procedures, CRF production, data management, data analysis) but also more conceptual in the context of protocol design, interpretation and discussion of the results and paper writing.

Within these different projects, I enriched my knowledge about epilepsy and epilepsy research in humans from different points of view.

In particular, I learned about different diagnostic, prognostic and therapeutic aspects of the disease. Furthermore, I learned to apply different methodologies to investigate the diagnosis, frequency, prognosis and treatment of epilepsy in an evidence-based perspective.

7. References

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8. Supplementary tables

Supplemetary table 3.3.1. Patient questionnaire. PNES vs. ES: list of variables with sensitivity or specificity less than 60.

Variable	PNES			ES			SE	SP	p-value
	Present	Absent	Not indicated	Present	Absent	Not indicated			
Trigger	11	3	3	6	4	1	78.6	40.0	0.3926
" tired	9	8	.	6	5	.	45.4	52.9	1.0000
" alcohol	4	13	.	0	11	.	23.4	100.0	0.1324
" sleep deprived	9	8	.	7	4	.	36.36	52.94	0.7047
" menses	0	17	.	3	8	.	0.00	72.73	0.0504
" emotion	12	5	.	7	4	.	70.59	36.36	1.0000
" pain	6	11	.	0	11	.	35.29	100.00	0.0549
Warning	14	1	2	7	0	4	93.33	0.00	1.0000
" fast deep breath	8	9	.	2	9	.	47.06	81.82	0.2264
" nausea	5	12	.	1	10	.	29.41	90.91	0.3547
" headache	8	9	.	2	9	.	47.06	81.82	0.2264
" upset	4	13	.	1	10	.	23.53	90.91	0.6195
" angry	1	16	.	1	10	.	5.88	90.91	1.0000

"	irritable	5	12	.	0	11	.	29.41	100.00	0.1247
"	anxious	9	8	.	6	5	.	52.94	54.55	1.0000
"	sad	4	13	.	1	10	.	23.53	90.91	0.6195
"	afraid	8	9	.	2	9	.	47.06	81.82	0.2264
"	physical pain	5	12	.	0	11	.	29.41	100.00	0.1247
"	déjà vu	4	13	.	2	9	.	23.53	81.82	1.0000
"	bad smell	2	15	.	0	11	.	11.76	100.00	0.5053
"	metallic taste	4	13	.	1	10	.	23.53	90.91	0.6195
"	coloured spots	6	11	.	1	10	.	35.29	90.91	0.1914
"	visual image	1	16	.	0	11	.	5.88	100.00	1.0000
"	sounds	4	13	.	0	11	.	23.53	100.00	0.1324
During seizure										
"	" aware able to respond	7	10	.	3	8	.	41.18	72.73	0.6888
"	" aware unable to respond	7	10	.	3	8	.	41.18	72.73	0.6888
"	" not aware	11	6	.	10	1	.	64.71	9.09	0.1914
"	" bite side tongue	8	9	.	4	7	.	47.06	63.64	0.7047
"	" bite tip tongue	2	15	.	2	9	.	11.76	81.82	1.0000

	" "	wet yourself	6	11	.	2	9	.	35.29	81.82	0.4188
	" "	lose bowel control	1	16	.	0	11	.	5.88	100.00	1.0000
	" "	severe injury	4	13	.	0	11	.	23.53	100.00	0.1324
After seizure											
	" "	trouble remembering	14	3	.	10	1	.	82.35	9.09	1.0000
	" "	trouble recognising people	7	10	.	4	7	.	41.18	63.64	1.0000
	" "	trouble understanding	12	5	.	6	5	.	70.59	45.45	0.4443
	" "	headache	16	0	.	7	4	.	100.00	36.36	0.0188
	" "	normal	1	16	.	4	7	.	5.88	63.64	0.0618
	" "	exhausted	15	2	.	9	2	.	88.24	18.18	1.0000
	" "	confused	10	7	.	8	3	.	58.82	27.27	0.6888
	" "	emotional	7	10	.	5	6	.	41.18	54.55	1.0000
Remote history											
	" "	Febrile seizures	1	16	.	1	10	.	5.88	90.91	1.0000
	" "	Brain infection	1	16	.	3	8	.	5.88	72.73	0.2694
	" "	Stroke	2	15	.	3	8	.	11.76	72.73	0.3531
	" "	Other neurol. illness/injury	4	13	.	1	10	.	23.53	90.91	0.6195

" "	Death of close relative	8	9	.	4	7	.	47.06	63.64	0.7047
" "	Neglect	5	12	.	3	8	.	29.41	72.73	1.0000
" "	Sexual abuse	5	12	.	2	9	.	29.41	81.82	0.6683
" "	Exposure to violence	9	8	.	5	6	.	52.94	54.55	1.0000
Last 6 months history										
" "	Head injury	4	13	.	0	11	.	23.53	100.00	0.1324
" "	Brain infection	0	17	.	0	11	.	5.88	100.00	1.0000
" "	Other neurol. illness/injury	2	15	.	1	10	.	11.76	90.91	1.0000
" "	New health problem	7	10	.	1	10	.	41.18	90.91	0.0987
" "	Worsening health problem	6	11	.	1	10	.	35.29	90.91	0.1914
" "	Surgery	5	12	.	1	10	.	29.41	90.91	0.3547
" "	Increase family demands	2	15	.	1	10	.	11.76	90.91	1.0000
" "	Job change	2	15	.	3	8	.	11.76	72.73	0.3531
" "	Divorce/separation	2	15	.	1	10	.	11.76	90.91	1.0000
" "	Loss of contact with close relative/friend	3	14	.	2	9	.	17.65	81.82	1.0000
" "	Neglect	1	16	.	1	10	.	5.88	90.91	1.0000
" "	Physical abuse	2	15	.	1	10	.	11.76	90.91	1.0000

" "	Sexual abuse	1	16	.	0	11	.	5.88	100.00	1.0000
" "	Emotional abuse	2	15	.	2	9	.	11.76	81.82	1.0000
" "	Re-exposure to former abuser	3	14	.	1	10	.	17.65	90.91	1.0000
" "	Exposure to violence	3	14	.	1	10	.	17.65	90.91	1.0000
Past symptoms										
" "	Joint stiffness	2	4	11	1	6	4	33.33	85.71	0.5594
" "	Nausea/vomiting	2	4	11	0	7	4	33.33	100.00	0.1923
" "	Constipation/diarrhoea	2	4	11	0	7	4	33.33	100.00	0.1923
" "	Pain with menses/sex/urination	0	6	11	0	7	4	.	100.00	ND
Past diagnosis										
" "	Low blood pressure	5	12	.	0	11	.	29.41	100.00	0.1247
" "	Sleep apnea	2	4	11	0	7	4	33.33	100.00	0.1923
" "	Irritable bowel syndrome	2	15	.	1	10	.	11.76	90.91	1.0000
" "	Crohn disease	0	6	11	0	7	4	.	100.00	ND
" "	Brain tumor	1	16	.	3	8	.	5.88	72.73	0.2694
" "	TBI	2	15	.	0	11	.	11.76	100.00	0.5053
" "	Chronic pain syndrome	2	15	.	0	11	.	11.76	100.00	0.5053

" "	Chronic fatigue syndrome	1	16	.	0	11	.	5.88	100.00	1.0000
" "	Fibromyalgia	4	13	.	0	11	.	23.53	100.00	0.1324
" "	Pnes	4	13	.	0	11	.	23.53	100.00	0.1324
Past surgeries										
" "	Brain surgery	2	15	.	3	8	.	11.76	72.73	0.3531
" "	Neck/back surgery	2	15	.	0	11	.	11.76	100.00	0.5053
" "	Cholecistectomy	6	11	.	1	10	.	35.29	90.91	0.1914
" "	Exploratory laparoscopy	4	13	.	0	11	.	23.53	100.00	0.1324
" "	Hysterectomy	2	15	.	1	10	.	11.76	90.91	1.0000
" "	Carpal tunnel surgery	1	16	.	0	11	.	5.88	100.00	1.0000
Education history										
" "	Learning disability	6	11	.	3	7	1	35.29	70.00	1.0000
" "	School additional help	5	12	.	3	8	.	29.41	72.73	1.0000
" "	Work	4	13	.	2	9	.	23.53	81.82	1.0000
" "	Applying for disability	8	9	.	9	2	.	47.06	18.18	0.1150
" "	On disability payments	6	10	1	0	11	.	37.50	100.00	0.0536
Psychiatric history										

" "	Depression	6	11	.	1	10	.	35.29	90.91	0.1914
" "	Anxiety	5	12	.	1	10	.	29.41	90.91	0.3547
" "	Bipolar illness	1	16	.	1	10	.	5.88	90.91	1.0000
" "	Borderline personality	1	16	.	0	11	.	5.88	100.00	1.0000
" "	Schizophrenia	0	17	.	0	11	.	.	100.00	ND
" "	Conversion disorder	0	17	.	0	11	.	.	100.00	ND
" "	ADHD	3	14	.	0	11	.	17.65	100.00	0.2579
" "	Counseling or therapy	13	4	.	6	5	.	76.47	45.45	0.4087
" "	Hospitalization for emotional/behavioural problems	3	14	.	1	10	.	17.65	90.91	1.0000
" "	Medications for emotional/behavioural problems	8	9	.	1	9	1	47.06	90.00	0.0912

Legend: PNES psychogenic non-epileptic seizures; ES epileptic seizures; SE sensitivity; SP specificity.

Supplementary table 3.3.2. Witness questionnaire. PNES vs. ES: list of variables with sensitivity or specificity less than 60.

Variable		PNES			ES			SE	SP	p-value
		Present	Absent	Not indicated	Present	Absent	Not indicated			
Seizure onset										
" "	stopping/staring	3	3	.	8	2	.	50.00	20.00	0.2995
" "	high-pitched cry	1	5	.	2	8	.	16.67	80.00	1.0000
" "	humming/vocalization	1	5	.	1	9	.	16.67	90.00	1.0000
" "	change feeling/sensation	2	4	.	2	8	.	33.33	80.00	0.6044
" "	odd smell	0	6	.	0	10	.	.	100.00	ND
" "	odd taste	0	6	.	0	10	.	.	100.00	ND
" "	deja vu	0	6	.	1	9	.	0.00	90.00	1.0000
" "	visual image	1	5	.	0	10	.	16.67	100.00	0.3750
" "	tunnel vision	0	6	.	0	10	.	.	100.00	ND
" "	blurred vision	1	5	.	0	10	.	16.67	100.00	0.3750
" "	nausea	1	5	.	1	9	.	16.67	90.00	1.0000
" "	abdominal rising sensation	0	6	.	0	10	.	.	100.00	ND

" "	tingling numbness	1	5	.	0	10	.	16.67	100.00	0.3570
" "	pain	0	6	.	0	10	.	.	100.00	ND
" "	heart racing	0	6	.	1	9	.	0.00	90.00	1.0000
" "	dizziness	2	4	.	0	10	.	33.33	100.00	0.1250
" "	other	2	4	.	2	8	.	33.33	80.00	0.6044
During seizure										
" "	shaking/stiffening	6	0	.	10	0	.	100.00	.	ND
" "	sudden	3	3	0	1	7	2	50.00	12.50	0.2448
" "	gradual build-up	3	3	0	1	7	2	50.00	12.50	0.2448
" "	one side only	1	5	0	1	8	1	16.67	88.89	1.0000
" "	both sides equally	2	4	0	6	3	1	66.67	33.33	1.0000
" "	alternating sides/same seizure	2	4	0	1	8	1	33.33	88.89	0.5253
" "	alt. sides in different seizures	0	6	0	0	9	1	.	100.00	ND
" "	sudden ending	1	4	1	2	8	.	20.00	80.00	1.0000
" "	gradual ending	1	4	1	3	7	.	80.00	30.00	1.0000
" "	not responsive at all	2	4	.	3	7	.	66.67	30.00	1.0000
" "	looks at but not responsive	0	6	.	1	9	.	0.00	90.00	1.0000

" "	speaks nonsense	2	4	.	0	10	.	33.33	100.00	0.1250
" "	speaks/follows commands	1	5	.	3	7	.	16.67	70.00	1.0000
" "	head turning to one side	2	4	0	3	6	1	33.33	66.67	1.0000
" "	eyes open	3	3	0	9	0	1	50.00	0.00	0.0440
" "	staring	2	4	.	6	4	.	33.33	40.00	0.6084
" "	wandering around	1	5	.	3	7	.	16.67	70.00	1.0000
" "	picking at things	0	6	.	4	6	.	0.00	60.00	0.2335
" "	one arm ben/stretched	2	4	.	3	7	.	33.33	70.00	1.0000
" "	brief jerks arms legs	2	4	.	3	7	.	66.67	30.00	1.0000
" "	agitated behaviour	1	5	.	1	9	.	16.67	90.00	1.0000
" "	making loud noises	0	6	.	2	8	.	0.00	80.00	0.5000
" "	sobbing/crying	2	4	.	0	10	.	33.33	100.00	0.1250
" "	trashing/flopping	2	4	.	3	7	.	33.33	70.00	1.0000
" "	out of sync limb movements	2	4	.	3	7	.	33.33	70.00	1.0000
" "	back arching	1	5	.	2	8	.	16.67	80.00	1.0000
" "	hip trusting	0	6	.	0	10	.	0.00	100.00	ND
" "	normal breathing	2	4	.	5	5	.	33.33	50.00	0.6329

" "	fast/heavy breathing	1	5	.	3	7	.	16.67	70.00	1.0000
" "	patient falling	3	2	1	6	3	1	60.00	33.33	1.0000
" "	slow, gradual slumping	0	5	1	0	9	1	0.00	100.00	ND
" "	sudden stiff/toppling over	1	4	1	1	8	1	20.00	88.89	1.0000
" "	< 2 min. duration	3	3	.	7	3	.	50.00	30.00	0.6066
End of seizure										
" "	cough	1	5	.	2	8	.	16.67	80.00	1.0000
" "	wiping nose	1	5	.	1	9	.	16.67	90.00	1.0000
" "	noisy/congested breathing	2	4	.	4	6	.	33.33	60.00	1.0000
" "	deeply asleep	1	5	.	1	9	.	16.67	90.00	1.0000
" "	awake confused/disoriented	4	2	.	8	2	.	66.67	20.00	0.6044
" "	normal	2	4	.	3	7	.	33.33	70.00	1.0000

Legend: PNES psychogenic non-epileptic seizures; ES epileptic seizures; SE sensitivity; SP specificity.

Supplementary Table 5.1. Age and sex distribution of the population of the study area (Lecco province) comparing participating general practitioners (GPs) to GPs who declined participation

Variable	Total population			Participating GPs' population			Declining GPs' population		
	N	%	95% CI	N	%	95% CI	N	%	95% CI
Sex									
M	165,.211	49.02	48.85-49.18	71,541	48.83	48.58-49.09	101,521	49.15	48.93-49.36
F	171,851	50.98	50.82-51.15	74,965	51.17	50.91-51.42	105,036	50.85	50.64-51.07
Total	337,062	100.00	100.00-100.00	146,506	100.00	100.00-100.00	206,557	100.00	100.00-100.00
Age, years (M)									
<15	24,455	7.26	7.17-7.34	15,700	10.72	10.56-10.87	10,073	4.88	4.78-4.97
15-34	38,181	11.33	11.22-11.43	15,361	10.48	10.33-10.64	24,665	11.94	11.80-12.08
35-54	53,190	15.78	15.66-15.90	21,380	14.59	14.41-14.77	34,297	16.60	16.44-16.76
55-74	37,791	11.21	11.11-11.32	14,920	10.18	10.03-10.34	24,523	11.87	11.73-12.01
75+	11,594	3.44	3.38-3.50	4,180	2.85	2.77-2.94	7,963	3.86	3.77-3.94
Age, years (F)									
<15	23,558	6.99	6.90-7.08	15,152	10.34	10.19-10.50	9,693	4.69	4.60-4.78
15-34	36,544	10.84	10.74-10.95	15,214	10.38	10.23-10.54	23,065	11.17	11.03-11.30
35-54	50,656	15.03	14.91-15.15	20,960	14.31	14.13-14.49	32,099	15.54	15.38-15.70
55-74	39,967	11.86	11.75-11.97	15,868	10.83	10.67-10.99	25,889	12.53	12.39-12.68
75+	21,126	6.27	6.19-6.35	7,771	5.30	5.19-5.42	14,290	6.92	6.81-7.03
Age, years (total)									
<15	48,013	14.24	14.13-14.36	30,852	21.06	20.85-21.27	19,766	9.57	9.44-9.70
15-34	74,725	22.17	22.03-22.31	30,575	20.87	20.66-21.08	47,730	23.11	22.93-23.29
35-54	103,846	30.81	30.65-30.97	42,340	28.90	28.67-29.13	66,396	32.14	31.94-32.35
55-74	77,758	23.07	22.93-23.21	30,788	21.01	20.81-21.22	50,412	24.41	24.22-24.59
75+	32,720	9.71	9.61-9.81	11,951	8.16	8.02-8.30	22,253	10.77	10.64-10.91

Legend: 95% CI = 95% Confidence Interval; F = Female; M = Male.

Supplementary Table 5.2. Age and sex-specific frequencies of the main syndromic categories in patients with DRE.

Syndromes	**0-14y**	**15-34y**	**35-54y**	**55-74y**	**75+y**	**Total**
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Women						
PI	0. (0.00)	1 (100.00)	0. (0.00)	0. (0.00)	0. (0.00)	1 (1.47)
PS	4 (15.38)	4 (15.38)	11 (42.31)	7 (26.92)	0 (0.00)	26 (38.24)
PC	1 (6.25)	6 (37.50)	5 (31.25)	4 (25.00)	0 (0.00)	16 (23.53)
GI	1 (12.50)	2 (25.00)	4 (50.00)	1 (12.50)	0 (0.00)	8 (11.76)
GC/GS	6 (50.00)	1 (8.33)	3 (25.00)	2 (16.67)	0 (0.00)	12 (17.65)
Undetermined	2 (50.00)	1 (25.00)	0 (0.00)	1 (25.00)	0 (0.00)	4 (5.88)
Special	0 (0.00)	1 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.47)
Total	14 (20.59)	16 (23.53)	23 (33.82)	15 (22.06)	0 (0.00)	68 (100.00)

Men						
PI	0. (0.00)	0. (0.00)	0. (0.00)	0. (0.00)	0. (0.00)	0. (0.00)
PS	3 (16.67)	3 (16.67)	7 (38.89)	4 (22.22)	1 (5.56)	18 (46.15)
PC	1 (14.29)	1 (14.29)	4 (57.14)	1 (14.29)	0. (0.00)	7 (17.95)
GI	1 (25.00)	1 (25.00)	1 (25.00)	0. (0.00)	1 (25.00)	4 (10.26)
GC/GS	5 (62.50)	2 (25.00)	1 (12.50)	0. (0.00)	0. (0.00)	8 (20.51)
Undetermined	0. (0.00)	0. (0.00)	0. (0.00)	1 (100.00)	0. (0.00)	1 (2.56)
Special	0. (0.00)	0. (0.00)	1 (100.00)	0. (0.00)	0. (0.00)	1 (2.56)
Total	10 (25.54)	7 (17.95)	14 (35.90)	6 (15.38)	2 (5.13)	39 (100.00)

Legend: PI = Partial Idiopathic; PS = Partial Symptomatic; PC = Partial Cryptogenic; GI = Generalized Idiopathic; GC/GS = Generalized Cryptogenic/Generalized Symptomatic; y= years.

Supplementary Table 5.3. Age, sex, and epilepsy syndrome distribution in prevalent and incident cases

Variable	Prevalent cases		Incident cases		p value
	N	%	N	%	
Sex					
M	193	47.65	188	54.97	0.0463
F	212	52.35	154	45.03	
Age, years					
<15	198	49.13	120	35.09	<0.0001
15-34	113	28.04	70	20.47	
35-54	58	14.39	62	18.13	
55-74	31	7.69	69	20.18	
75+	3	0.74	21	6.14	
Epilepsy syndrome					
GC/GS	41	10.12	33	9.65	0.3988
GI	95	23.46	59	17.25	
PC	89	21.98	78	22.81	
PI	31	7.65	23	6.73	
PS	132	32.59	133	38.89	
Special	3	0.74	4	1.17	
Undetermined	14	3.46	12	3.51	
Drug resistant					
No	334	82.5	306	89.5	0.0065
Yes	71	17.5	36	10.5	

Legend: F = Female; M = Male; GC/GS = Generalized Cryptogenic/Generalized Symptomatic; PC = Partial Cryptogenic; PI = Partial Idiopathic; PS = Partial Symptomatic.

Supplementary Table 5.4. General characteristics of the sample by age group

Variable	Category	Age <18		Age 18+		p-value
		N	%	N	%	
Gender	F	185	52.9	179	45.3	0.0399
	M	165	47.1	216	54.7	
Family history of seizures	Yes	74	21.1	37	9.4	<0.0001
	No	253	72.3	331	83.8	
	Unknown	23	6.6	27	6.8	
Seizures	Partial	187	53.4	271	68.6	<0.0001
	Generalized	154	44.0	106	26.8	
	Unclassifiable	9	2.6	18	4.6	
Syndrome	GC/GS	47	13.4	27	6.8	<0.0001
	GI	97	27.7	57	14.4	
	PC	52	14.9	113	28.6	
	PI	49	14.0	5	1.3	
	PS	90	25.7	175	44.3	
	Undetermined	10	2.9	16	4.1	
	Special	5	1.4	2	0.5	
Disease duration at diagnosis	<1y	317	90.6	349	88.6	0.3758
	≥1 y	33	9.4	45	11.4	
	Missing			1		

Number of AED	0	9	2.6	7	1.8	0.0125
	1	171	48.9	220	55.7	
	2	88	25.1	111	28.1	
	3+	82	23.4	57	14.4	
Drug resistant	No	276	78.9	362	91.7	<0.0001
	Yes	74	21.1	33	8.3	

Legend: F = Female; M = Male; GC/GS = Generalized Cryptogenic/Generalized Symptomatic; GI = Generalized Idiopathic; PC = Partial Cryptogenic; PI = Partial Idiopathic; PS = Partial Symptomatic; y = Years; AED = antiepileptic drug.

Supplementary Table 5.5. Cause specific cumulative probabilities of withdrawal of the first, second and third AED.

			Ineffectiveness		Adverse events		Terminal remission		Other	
	Year	**Number at risk***	**n**	**CIF*100**	**n**	**CIF*100**	**n**	**CIF*100**	**n**	**CIF*100**
First AED	1	664	21	2.9	4	0.5	7	1.0	2	0.2
	3	571	39	5.6	7	1.3	22	3.2	10	1.4
	5	459	51	7.6	13	2.0	59	9.3	17	2.6
	10	307	66	10.4	16	2.5	93	15.7	26	4.4
	20	175	75	12.6	19	3.3	109	20.0	35	6.6
Second AED	1	288	14	4.3	9	2.7	1	0.3	5	1.5
	3	215	28	9.0	9	2.7	5	1.7	7	2.2
	5	165	33	11.1	10	3.2	8	3.1	10	3.6
	10	92	39	14.9	10	3.2	21	10.3	12	4.6
	20	44	40	15.8	11	4.3	24	13.3	15	7.7
Third AED	1	115	12	8.8	3	2.2	1	0.7	2	1.5
	3	75	20	15.8	4	3.0	2	1.6	4	3.4
	5	48	22	18.6	4	3.0	3	2.6	4	3.4
	10	25	28	29.8	4	3.0	4	4.3	5	5.0
	20	11	31	39.3	6	8.0	4	4.3	5	5.0

*Patients still in treatment for each specified time.
CIF*100 Cumulative incidence function*100; AED Antiepileptic drug.

Supplementary Table 5.6. Cause specific cumulative probabilities of withdrawal of the first, second and third drug, by old and new AEDs.

				Ineffectiveness		Adverse effects		Terminal remission		Other	
		Year	Number at risk*	n	CIF*100	n	CIF*100	n	CIF*100	n	CIF*100
First AED	New AEDs	1	48	1	1.7	0	0.0	0	0.0	0	0.0
		3	34	4	8.7	0	0.0	2	4.5	0	0.0
		5	16	6	15.6	1	2.5	5	14.0	1	3.5
		10	5	8	26.9	1	2.5	7	25.2	2	9.0
		20	5	8	26.9	1	2.5	7	25.2	2	9.0
	Old AEDs	1	616	20	3.0	4	0.6	7	1.1	2	0.3
		3	537	35	5.4	7	1.1	20	3.2	10	1.6
		5	443	45	7.1	12	1.9	54	9.0	16	2.6
		10	302	58	9.6	15	2.5	86	15.3	24	4.2
		20	170	67	12.0	18	3.3	102	19.7	33	6.6
p-value					0.1058		0.9122		0.2738		0.9036
Second AED	New AEDs	1	84	5	5.1	2	1.9	1	1.0	3	3.0
		3	45	13	15.0	2	1.9	2	2.3	3	3.0
		5	30	13	15.0	2	1.9	3	4.7	3	3.0
		10	11	16	27.5	2	1.9	5	12.3	3	3.0
		20	5	16	27.5	2	1.9	5	12.3	4	12.1
	Old AEDs	1	204	9	4.0	7	3.1	0	0.0	2	0.9
		3	170	15	6.8	7	3.1	3	1.5	4	1.9
		5	135	20	9.4	8	3.6	5	2.6	7	1.4
		10	81	23	11.7	8	3.6	16	10.0	9	4.8
		20	39	24	12.6	9	4.9	19	13.2	11	7.1

		p-value			0.0765		0.4509		0.8685		0.4086
Third AED	**New AEDs**	**1**	56	4	6.2	2	3.1	0	0.0	0	0.0
		3	35	6	10.6	3	5.1	0	0.0	1	2.3
		5	18	8	18.1	3	5.1	0	0.0	1	2.3
		10	7	12	38.2	3	5.1	1	4.7	2	5.4
		20	1	15	74.7	4	14.2	1	4.7	2	5.4
	Old AEDs	**1**	59	8	11.1	1	1.4	1	1.4	2	2.8
		3	40	14	20.3	1	1.4	2	2.8	3	4.5
		5	30	14	20.3	1	1.4	3	4.7	3	4.5
		10	18	16	26.5	1	1.4	3	4.7	3	4.5
		20	11	16	26.5	2	4.9	3	4.7	3	4.5
		p-value			0.4046		0.1829		0.4717		0.8666

*Patients still in treatment for each specified time.

CIF*100 Cumulative incidence function*100; AED Antiepileptic drug.

Supplementary Table 5.7. Drug daily doses (median and range) of first AED given to children (<15 years) (A) and adults (≥15 years) (B).

A. <15 years

	Total			Ineffectiveness			Adverse events		
	Median	**Min**	**Max**	**Median**	**Min**	**Max**	**Median**	**Min**	**Max**
BSC	-	-	-	-	-	-	-	-	-
CBZ	750	150	2400	800	340	1500	800	800	800
CLB	10	10	10	10	10	10	-	-	-
CNP	-	-	-	-	-	-	-	-	-
ESM	450	300	600	-	-	-	-	-	-
GBP	100	100	100	100	100	100	-	-	-
LEV	925	750	1100	-	-	-	-	-	-
LTG	-	-	-	-	-	-	-	-	-
OXC	750	300	1500	-	-	-	-	-	-
PB	100	30	250	100	45	100	-	-	-
PGB	-	-	-	-	-	-	-	-	-
PHT	300	100	400	100	100	100	-	-	-
PRM	-	-	-	-	-	-	-	-	-
TGB	-	-	-	-	-	-	-	-	-
TPM	550	100	1000	-	-	-	-	-	-
VGB	1400	1250	2000	-	-	-	-	-	-
VPA	700	200	1900	650	300	1000	-	-	-
VPM	250	200	300	-	-	-	-	-	-
ZNS	-	-	-	-	-	-	-	-	-

BSC Barbexaclone, CBZ Carbamazepine, CLB Clobazam, CNP Clonazepam, ESM Ethosuximide, GBP Gabapentin, LEV Levetiracetam, LTG Lamotrigine, OXC Oxcarbazepine, PB Phenobarbital, PHT Phenytoin, PGB Pregabalin, PRM Primidone, TGB Tiagabine, TPM Topiramate, VGB Vigabatrin, VPA Valproate.

A. ≥15 years

	Total			Ineffectiveness			Adverse events		
	Median	**Min**	**Max**	**Median**	**Min**	**Max**	**Median**	**Min**	**Max**
BSC	175	100	250	100	100	100			
CBZ	600	100	2400	800	400	1200	700	400	1000
CLB	-	-	-	-	-	-	-	-	-
CNP	1	1	1	-	-	-	-	-	-
ESM	-	-	-	-	-	-	-	-	-
GBP	600	600	600	-	-	-	-	-	-
LEV	1000	500	2250	-	-	-	-	-	-
LTG	200	75	300	75	75	75	-	-	-
OXC	900	100	1500	1050	600	1500	600	600	600
PB	100	50	300	100	100	150	100	50	100
PGB	-	-	-	-	-	-	-	-	-
PHT	275	100	400	150	100	400	250	250	250
PRM	-	-	-	-	-	-	-	-	-
TGB	-	-	-	-	-	-	-	-	-
TPM	300	300	300	-	-	-	-	-	-
VGB	-	-	-	-	-	-	-	-	-
VPA	1000	150	2500	650	500	1000	1325	1250	1400
VPM	-	-	-	-	-	-	-	-	-
ZNS	-	-	-	-	-	-	-	-	-

BSC Barbexaclone, CBZ Carbamazepine, CLB Clobazam, CNP Clonazepam, ESM Ethosuximide, GBP Gabapentin, LEV Levetiracetam, LTG Lamotrigine, OXC Oxcarbazepine, PB Phenobarbital, PHT Phenytoin, PGB Pregabalin, PRM Primidone, TGB Tiagabine, TPM Topiramate, VGB Vigabatrin, VPA Valproate.

9. Appendix

9.1. MI-RO Patient Questionnaire

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Demographics

Please complete the survey below.

Thank you!

1) MIRO ID _____

Demographic Characteristics

2) Date subject signed consent _____ (YYYY-MM-DD)

3) Date of Interview _____ (YYYY-MM-DD)

4) First Name _____

5) Last Name _____

Contact Information

6) Street, City, State, ZIP _____

7) Phone number _____ (Include Area Code)

8) Second phone number _____ (Include Area Code)

9) E-mail _____

10) Gender
- ○ Female
- ○ Male

11) Ethnicity
- ○ Hispanic or Latino
- ○ NOT Hispanic or Latino
- ○ Unknown / Not Reported

12) Race
- ☐ American Indian/Alaska Native
- ☐ Asian
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ Black or African American
- ☐ White
- ☐ More Than One Race
- ☐ Unknown / Not Reported

13) Date of birth _____ (YYYY-MM-DD)

14) Age (years) _____

15) What is your marital status?
- ○ Single
- ○ Married/Partnered
- ○ Separated
- ○ Divorced
- ○ Widowed

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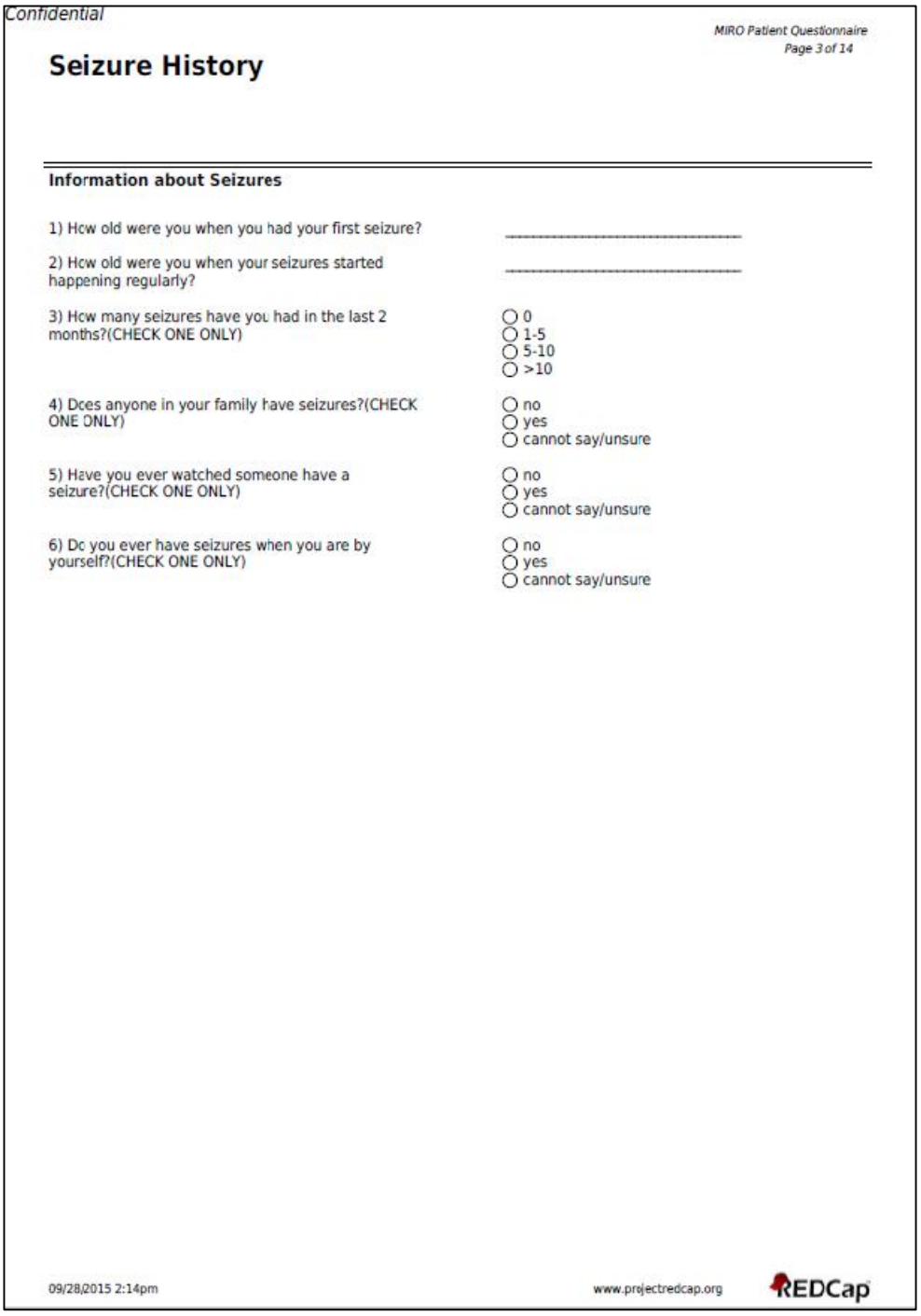
16) Who are you living with now?

- ○ Alone
- ○ Spouse/Partner
- ○ Parent
- ○ Extended Family
- ○ Housemates



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MIRO Patient Questionnaire
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Seizure History

Information about Seizures

1) How old were you when you had your first seizure?	_____
2) How old were you when your seizures started happening regularly?	_____
3) How many seizures have you had in the last 2 months?(CHECK ONE ONLY)	◯ 0 ◯ 1-5 ◯ 5-10 ◯ >10
4) Does anyone in your family have seizures?(CHECK ONE ONLY)	◯ no ◯ yes ◯ cannot say/unsure
5) Have you ever watched someone have a seizure?(CHECK ONE ONLY)	◯ no ◯ yes ◯ cannot say/unsure
6) Do you ever have seizures when you are by yourself?(CHECK ONE ONLY)	◯ no ◯ yes ◯ cannot say/unsure

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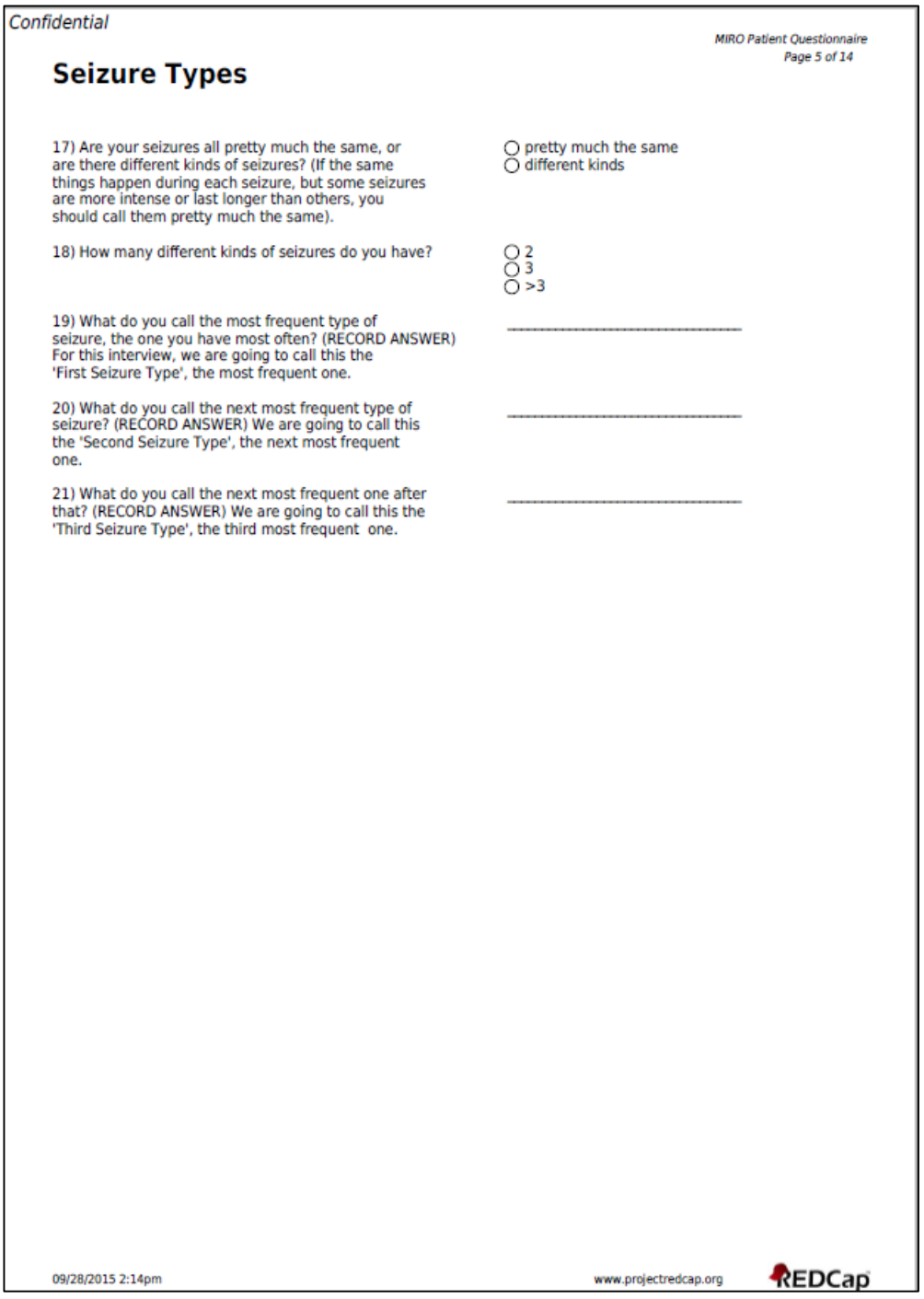
Seizure Triggers

7) Is there anything that seems to trigger or bring on any of your seizures?

- ○ no
- ○ yes
- ○ cannot say/unsure

How often are your seizures triggered by the following (CHECK ALL THAT APPLY)

	all of the time	most of the time	a good bit of the time	some of the time	none of the time
8) being tired	☐	☐	☐	☐	☐
9) after drinking alcohol	☐	☐	☐	☐	☐
10) being sleep deprived	☐	☐	☐	☐	☐
11) your menses	☐	☐	☐	☐	☐
12) strong emotions, anxiety or stress	☐	☐	☐	☐	☐
13) headaches	☐	☐	☐	☐	☐
14) other types of pain	☐	☐	☐	☐	☐
15) bright or flashing lights	☐	☐	☐	☐	☐
16) feeling overwhelmed	☐	☐	☐	☐	☐



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Seizure Types

17) Are your seizures all pretty much the same, or are there different kinds of seizures? (If the same things happen during each seizure, but some seizures are more intense or last longer than others, you should call them pretty much the same).

- ○ pretty much the same
- ○ different kinds

18) How many different kinds of seizures do you have?

- ○ 2
- ○ 3
- ○ >3

19) What do you call the most frequent type of seizure, the one you have most often? (RECORD ANSWER) For this interview, we are going to call this the 'First Seizure Type', the most frequent one.

_____

20) What do you call the next most frequent type of seizure? (RECORD ANSWER) We are going to call this the 'Second Seizure Type', the next most frequent one.

_____

21) What do you call the next most frequent one after that? (RECORD ANSWER) We are going to call this the 'Third Seizure Type', the third most frequent one.

_____

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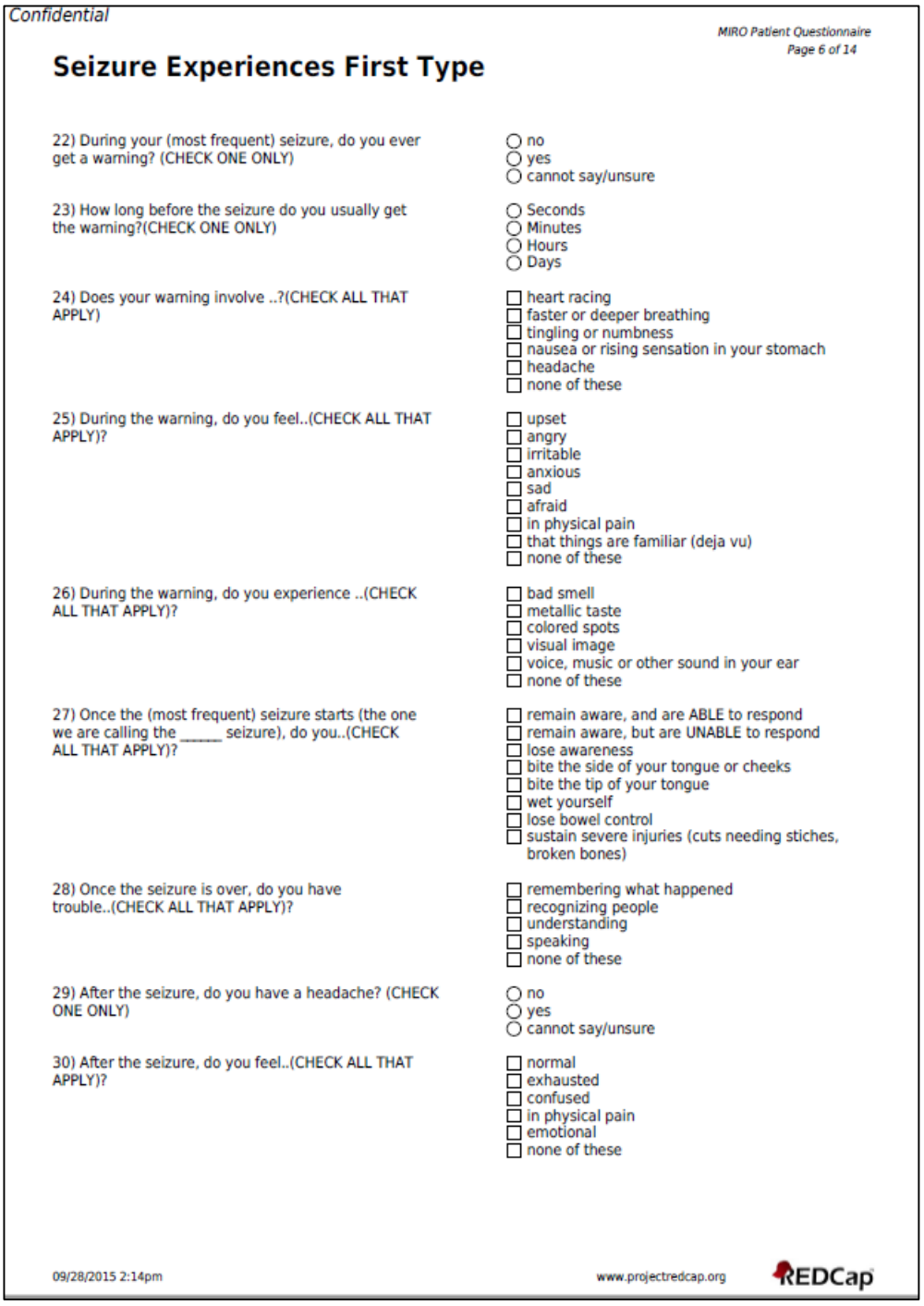

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Seizure Experiences First Type

22) During your (most frequent) seizure, do you ever get a warning? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

23) How long before the seizure do you usually get the warning?(CHECK ONE ONLY)
- ○ Seconds
- ○ Minutes
- ○ Hours
- ○ Days

24) Does your warning involve ..?(CHECK ALL THAT APPLY)
- ☐ heart racing
- ☐ faster or deeper breathing
- ☐ tingling or numbness
- ☐ nausea or rising sensation in your stomach
- ☐ headache
- ☐ none of these

25) During the warning, do you feel..(CHECK ALL THAT APPLY)?
- ☐ upset
- ☐ angry
- ☐ irritable
- ☐ anxious
- ☐ sad
- ☐ afraid
- ☐ in physical pain
- ☐ that things are familiar (deja vu)
- ☐ none of these

26) During the warning, do you experience ..(CHECK ALL THAT APPLY)?
- ☐ bad smell
- ☐ metallic taste
- ☐ colored spots
- ☐ visual image
- ☐ voice, music or other sound in your ear
- ☐ none of these

27) Once the (most frequent) seizure starts (the one we are calling the _____ seizure), do you..(CHECK ALL THAT APPLY)?
- ☐ remain aware, and are ABLE to respond
- ☐ remain aware, but are UNABLE to respond
- ☐ lose awareness
- ☐ bite the side of your tongue or cheeks
- ☐ bite the tip of your tongue
- ☐ wet yourself
- ☐ lose bowel control
- ☐ sustain severe injuries (cuts needing stiches, broken bones)

28) Once the seizure is over, do you have trouble..(CHECK ALL THAT APPLY)?
- ☐ remembering what happened
- ☐ recognizing people
- ☐ understanding
- ☐ speaking
- ☐ none of these

29) After the seizure, do you have a headache? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

30) After the seizure, do you feel..(CHECK ALL THAT APPLY)?
- ☐ normal
- ☐ exhausted
- ☐ confused
- ☐ in physical pain
- ☐ emotional
- ☐ none of these

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Seizure Experiences Second Type

Now let me ask you the same questions about your other types of seizures.

31) During your second most frequent seizure (the one we are calling the _____ seizure), do you ever get a warning? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

32) How long before the seizure do you usually get the warning?(CHECK ONE ONLY)
- ○ Seconds
- ○ Minutes
- ○ Hours
- ○ Days

33) Does your warning involve ..?(CHECK ALL THAT APPLY)
- ☐ heart racing
- ☐ faster or deeper breathing
- ☐ tingling or numbness
- ☐ nausea or rising sensation in your stomach
- ☐ headache

34) During the warning, do you feel..(CHECK ALL THAT APPLY)?
- ☐ upset
- ☐ angry
- ☐ irritable
- ☐ anxious
- ☐ sad
- ☐ afraid
- ☐ in physical pain
- ☐ that things are familiar (deja vu)

35) During the warning, do you experience ..(CHECK ALL THAT APPLY)?
- ☐ bad smell
- ☐ metallic taste
- ☐ colored spots
- ☐ visual image
- ☐ voice, music or other sound in your ear in your ear

36) Once this seizure starts, do you..(CHECK ALL THAT APPLY)?
- ☐ remain aware, and are ABLE to respond
- ☐ remain aware, but are UNABLE to respond
- ☐ lose awareness
- ☐ bite the side of your tongue or cheeks
- ☐ bite the tip of your tongue
- ☐ wet yourself
- ☐ lose bowel control
- ☐ sustain severe injuries (cuts needing stiches, broken bones)

37) Once the seizure is over, do you have trouble..(CHECK ALL THAT APPLY)?
- ☐ remembering what happened
- ☐ recognizing people
- ☐ understanding
- ☐ speaking

38) After the seizure, do you have a headache? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

39) After the seizure, do you feel..(CHECK ALL THAT APPLY)?
- ☐ normal
- ☐ exhausted
- ☐ confused
- ☐ in physical pain
- ☐ emotional

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MIRO Patient Questionnaire
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Seizure Experiences Third Type

Now let's talk about your third most frequent seizure type.

40) During your third most frequent seizure (the one we are calling the _____ seizure), do you ever get a warning? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

41) How long before the seizure do you usually get the warning?(CHECK ONE ONLY)
- ○ Seconds
- ○ Minutes
- ○ Hours
- ○ Days

42) Does your warning involve ..?(CHECK ALL THAT APPLY)
- ☐ heart racing
- ☐ faster or deeper breathing
- ☐ tingling or numbness
- ☐ nausea or rising sensation in your stomach
- ☐ headache

43) During the warning, do you feel..(CHECK ALL THAT APPLY)?
- ☐ upset
- ☐ angry
- ☐ irritable
- ☐ anxious
- ☐ sad
- ☐ afraid
- ☐ in physical pain
- ☐ that things are familiar (deja vu)

44) During the warning, do you experience ..(CHECK ALL THAT APPLY)?
- ☐ bad smell
- ☐ metallic taste
- ☐ colored spots
- ☐ visual image
- ☐ voice, music or other sound in your ear in your ear

45) Once this seizure starts, do you..(CHECK ALL THAT APPLY)?
- ☐ remain aware, and are ABLE to respond
- ☐ remain aware, but are UNABLE to respond
- ☐ lose awareness
- ☐ bite the side of your tongue or cheeks
- ☐ bite the tip of your tongue
- ☐ wet yourself
- ☐ lose bowel control
- ☐ sustain severe injuries (cuts needing stiches, broken bones)

46) Once the seizure is over, do you have trouble..(CHECK ALL THAT APPLY)?
- ☐ remembering what happened
- ☐ recognizing people
- ☐ understanding
- ☐ speaking

47) After the seizure, do you have a headache? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

48) After the seizure, do you feel..(CHECK ALL THAT APPLY)?
- ☐ normal
- ☐ exhausted
- ☐ confused
- ☐ in physical pain
- ☐ emotional

Risk Factors

Have any of the following things happened to you? If yes, how old were you when they first happened? (CHECK ALL THAT APPLY)

	younger than 5 years	5-10 years	10-16 years	older than 16 years
49) seizure with fever	☐	☐	☐	☐
50) head injury with loss of consciousness longer than 5 minutes	☐	☐	☐	☐
51) brain infection	☐	☐	☐	☐
52) stroke	☐	☐	☐	☐
53) other neurologic illness or injury	☐	☐	☐	☐
54) death of a parent or sibling	☐	☐	☐	☐
55) neglect	☐	☐	☐	☐
56) physical abuse	☐	☐	☐	☐
57) sexual abuse	☐	☐	☐	☐
58) emotional abuse	☐	☐	☐	☐
59) exposure to threats or violence	☐	☐	☐	☐
60) exposure to substance abuse in a close family member	☐	☐	☐	☐

Possible Seizure Precipitants

61) Did any of the following things happen in the 6 months before your seizures started happening regularly? (CHECK ALL THAT APPLY)

- ☐ head injury with loss of consciousness longer than 5 minutes
- ☐ brain infection
- ☐ stroke
- ☐ other neurologic illness or injury
- ☐ new health problem
- ☐ significant worsening of existing health problem
- ☐ surgery
- ☐ significant increase in family demands
- ☐ significant job change or change in job demands
- ☐ divorce/separation
- ☐ loss of contact with family member or loved one (death, moving away)
- ☐ neglect
- ☐ physical abuse
- ☐ sexual abuse
- ☐ emotional abuse
- ☐ re-exposure to former abuser
- ☐ exposure to threats or violence

Other Health History

Do you have any of the following symptoms? If so, has a doctor identified what is causing them?(CHECK ALL THAT APPLY)

	No	Yes-identified cause	Yes-but no identified cause
62) fatigue	☐	☐	☐
63) joint stiffness	☐	☐	☐
64) nausea or vomitting	☐	☐	☐
65) constipation or diarrhea	☐	☐	☐
66) pain with menses,sex or urination	☐	☐	☐

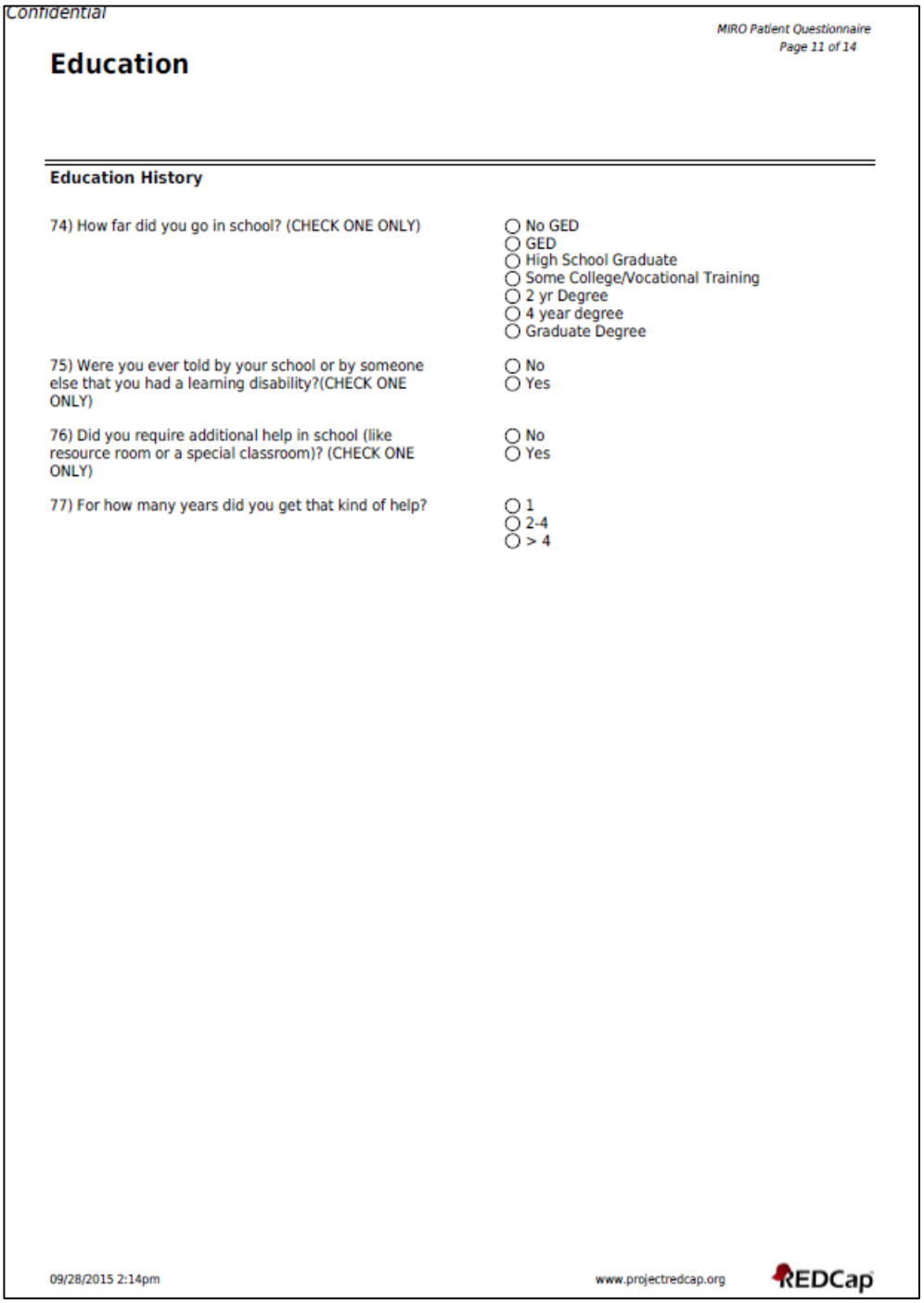
Other Diagnoses

67) Has a doctor ever told you that you have any of the following problems?(CHECK ALL THAT APPLY)

- ☐ Low Blood Pressure
- ☐ Sleep Apnea
- ☐ Irritable Bowel Syndrome
- ☐ Crohn's Disease
- ☐ Brain Tumor
- ☐ Traumatic Brain Injury
- ☐ GERD or 'reflux'
- ☐ Chronic Pain Syndrome
- ☐ Chronic Fatigue Syndrome
- ☐ Fibromyalgia
- ☐ Psychogenic,non-epileptic or pseudoseizures

Have you had any of these surgeries for problems other than seizures? If so, did the surgery help the problem?(CHECK ALL THAT APPLY)

	No	Yes-helped the problem	Yes-but did not help the problem
68) Brain surgery	☐	☐	☐
69) Back or neck surgery	☐	☐	☐
70) Cholecystectomy	☐	☐	☐
71) Exploratory laparoscopy	☐	☐	☐
72) Hysterectomy	☐	☐	☐
73) Carpal Tunnel Surgery	☐	☐	☐



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MIRO Patient Questionnaire
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Education

Education History

74) How far did you go in school? (CHECK ONE ONLY)

- ○ No GED
- ○ GED
- ○ High School Graduate
- ○ Some College/Vocational Training
- ○ 2 yr Degree
- ○ 4 year degree
- ○ Graduate Degree

75) Were you ever told by your school or by someone else that you had a learning disability?(CHECK ONE ONLY)

- ○ No
- ○ Yes

76) Did you require additional help in school (like resource room or a special classroom)? (CHECK ONE ONLY)

- ○ No
- ○ Yes

77) For how many years did you get that kind of help?

- ○ 1
- ○ 2-4
- ○ > 4

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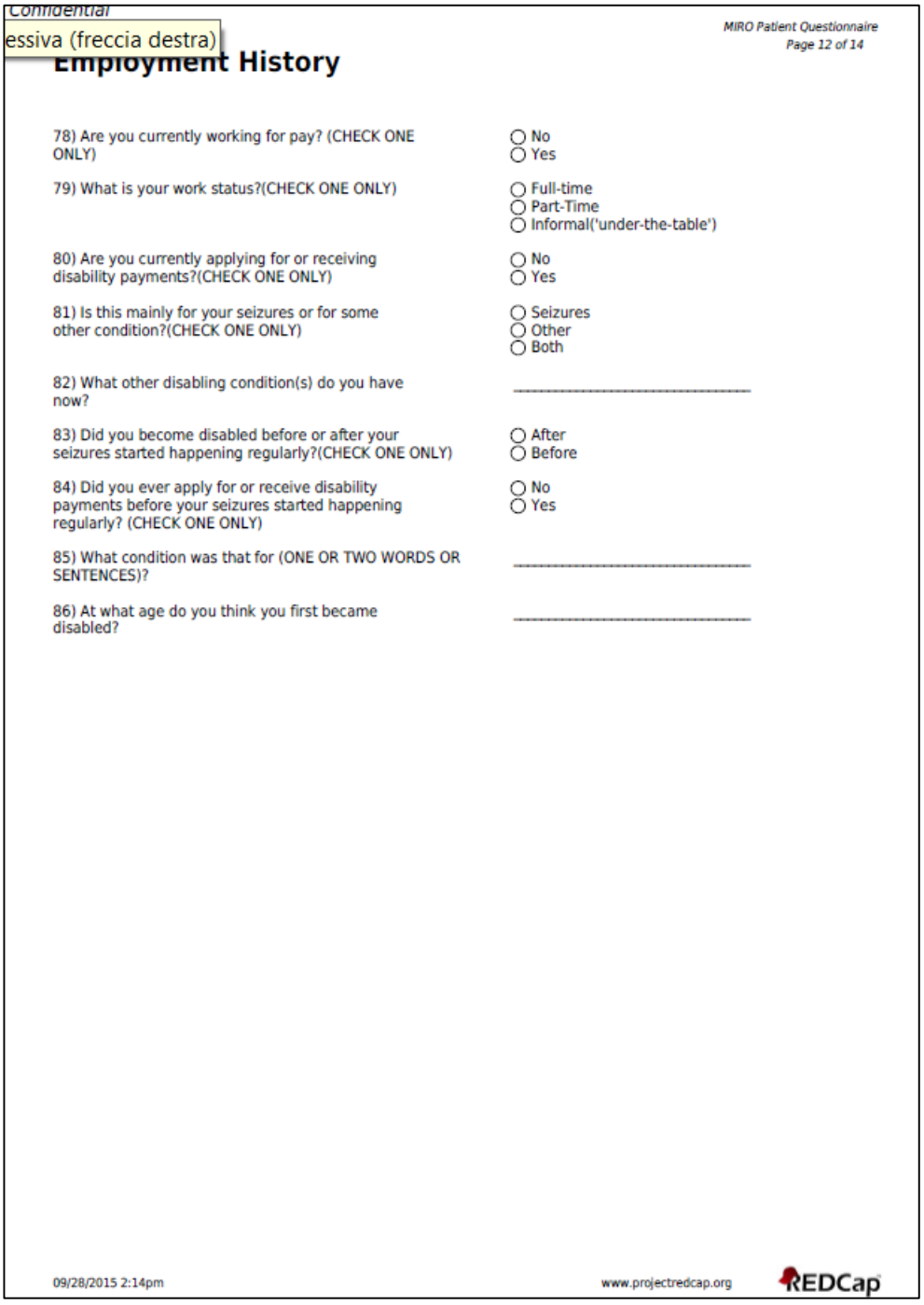

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MIRO Patient Questionnaire
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Employment History

78) Are you currently working for pay? (CHECK ONE ONLY)
- ○ No
- ○ Yes

79) What is your work status?(CHECK ONE ONLY)
- ○ Full-time
- ○ Part-Time
- ○ Informal('under-the-table')

80) Are you currently applying for or receiving disability payments?(CHECK ONE ONLY)
- ○ No
- ○ Yes

81) Is this mainly for your seizures or for some other condition?(CHECK ONE ONLY)
- ○ Seizures
- ○ Other
- ○ Both

82) What other disabling condition(s) do you have now? _____

83) Did you become disabled before or after your seizures started happening regularly?(CHECK ONE ONLY)
- ○ After
- ○ Before

84) Did you ever apply for or receive disability payments before your seizures started happening regularly? (CHECK ONE ONLY)
- ○ No
- ○ Yes

85) What condition was that for (ONE OR TWO WORDS OR SENTENCES)? _____

86) At what age do you think you first became disabled? _____

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Psychiatric History

87) BEFORE YOUR SEIZURES STARTED, had you ever been diagnosed or treated for any of the following problems? (CHECK ALL THAT APPLY)

- ☐ Depression
- ☐ Anxiety
- ☐ Bipolar Illness
- ☐ Borderline Personality
- ☐ Schizophrenia
- ☐ Conversion Disorder
- ☐ ADHD

88) Have you ever been in counseling or therapy? (CHECK ONE ONLY)

- ○ No
- ○ Yes

89) How many years were you in counseling or therapy? _____

90) Have you ever tried to hurt yourself (e.g., cutting, suicide gesture or attempt)? (CHECK ONE ONLY)

- ○ No
- ○ Yes

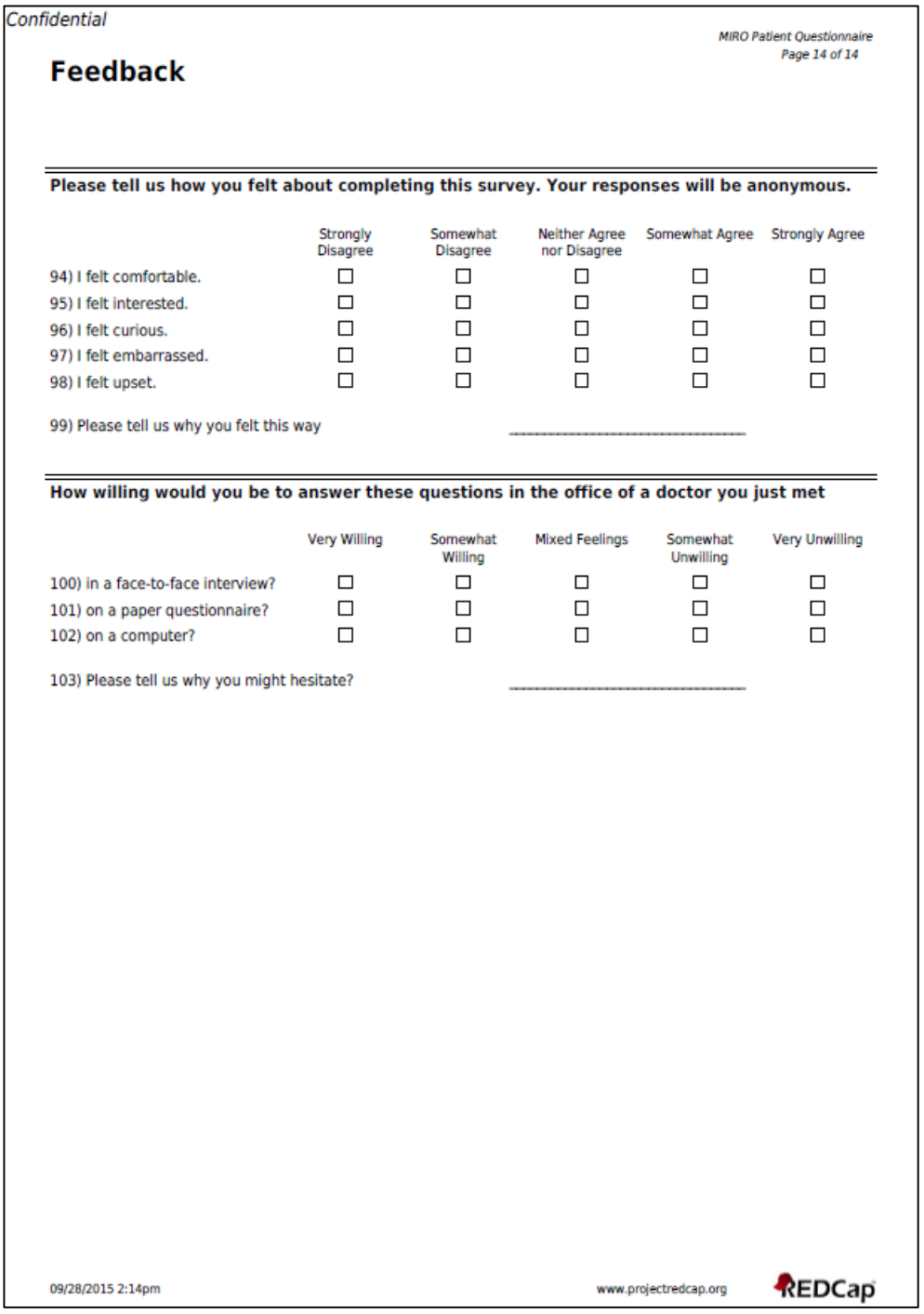
91) Were you ever admitted to the hospital for any other emotional or behavioral problem? (CHECK ONE ONLY)

- ○ No
- ○ Yes

92) Did you ever take medications for any of these or other emotional or behavioral problems?(CHECK ONE ONLY)

- ○ No
- ○ Yes

93) How many years did you take these medications? _____



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MIRO Patient Questionnaire
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Feedback

Please tell us how you felt about completing this survey. Your responses will be anonymous.

	Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree
94) I felt comfortable.	☐	☐	☐	☐	☐
95) I felt interested.	☐	☐	☐	☐	☐
96) I felt curious.	☐	☐	☐	☐	☐
97) I felt embarrassed.	☐	☐	☐	☐	☐
98) I felt upset.	☐	☐	☐	☐	☐

99) Please tell us why you felt this way _____

How willing would you be to answer these questions in the office of a doctor you just met

	Very Willing	Somewhat Willing	Mixed Feelings	Somewhat Unwilling	Very Unwilling
100) in a face-to-face interview?	☐	☐	☐	☐	☐
101) on a paper questionnaire?	☐	☐	☐	☐	☐
102) on a computer?	☐	☐	☐	☐	☐

103) Please tell us why you might hesitate? _____

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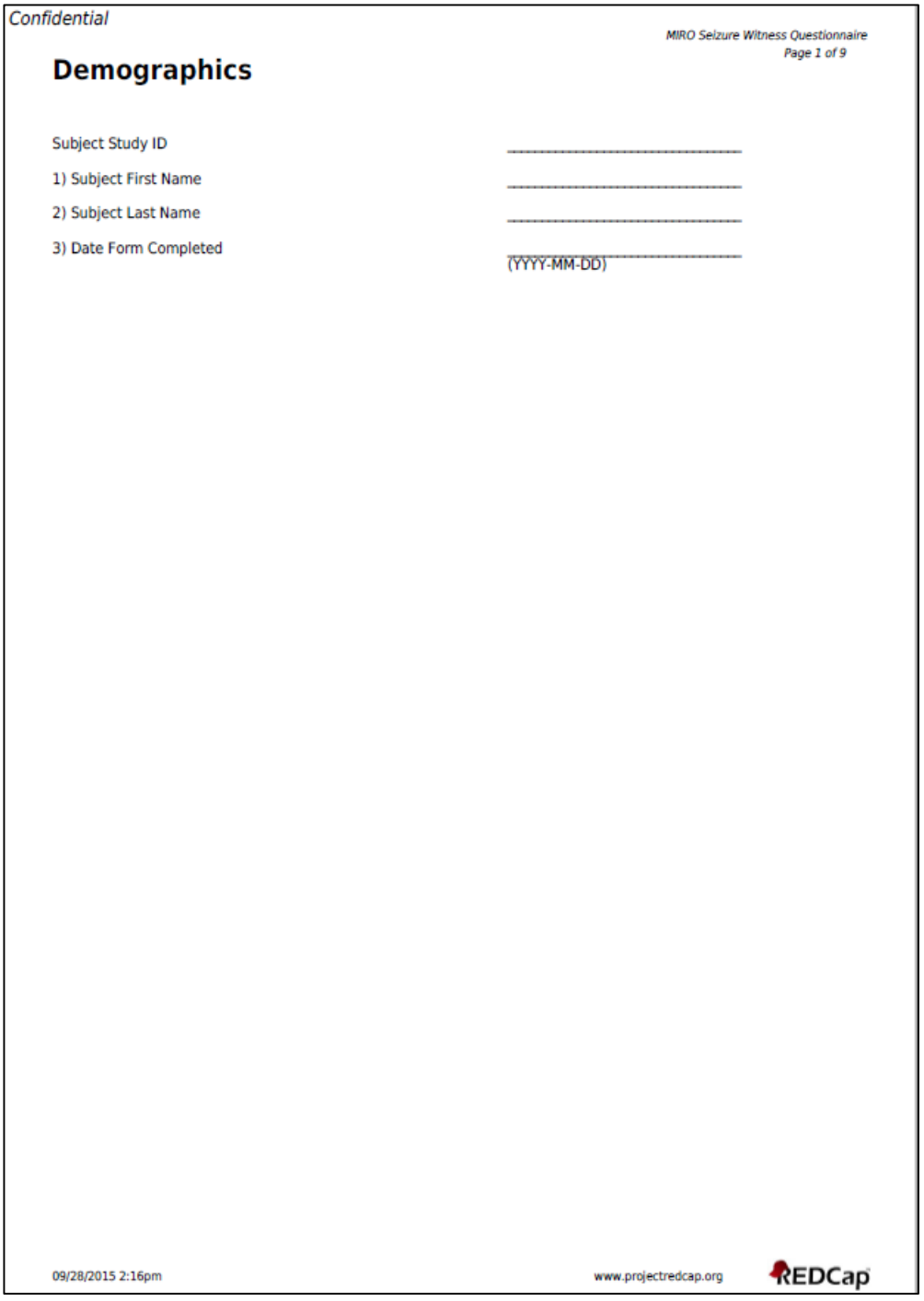
9.2. MI-RO Witness Questionnaire



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MIRO Seizure Witness Questionnaire
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Demographics

Subject Study ID _____

1) Subject First Name _____

2) Subject Last Name _____

3) Date Form Completed _____
(YYYY-MM-DD)

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MIRO Seizure Witness Questionnaire
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Seizure History

4) How often do you see the patient?
- ○ Daily
- ○ Several Times a Week
- ○ Every Few Weeks
- ○ Monthly
- ○ Less than Monthly

5) How many seizures have you witnessed?
- ○ 1-5
- ○ 5-10
- ○ >10

Now, I want you to tell me about what you see before, during and after the patient's seizure (or seizures, if they have more than one type). I want to know what YOU have seen, not what others have told you.

6) First of all, do all the seizures look pretty much the same, or have you seen different types of seizures? (If they look mostly the same, but some are more intense or last longer than others, you should call them pretty much the same.
- ○ Pretty Much the Same
- ○ Different Kinds

7) How many different types of seizures does the patient have?
- ○ 2
- ○ 3
- ○ >3

8) What do you call the most frequent type of seizure, the one you have seen most often? (RECORD ANSWER) For this interview, we are going to call this the 'First Seizure Type', the most frequent one.

_____

9) What do you call the next most frequent type of seizure? (RECORD ANSWER) We are going to call this the 'Second Seizure Type', the next most frequent one.

_____

10) What do you call the next most frequent one after that? (RECORD ANSWER) We are going to call this the 'Third Seizure Type', the third most frequent one.

_____

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MIRO Seizure Witness Questionnaire
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Seizure Behavior First Type

I'd like to ask you what you USUALLY see during the (first type of) seizure. Indicate 'yes' or check the box if you see it USUALLY, at least half the time.

11) Does this seizure type look the same each time, or different? (CHECK ONE ONLY)
- ○ same
- ○ different
- ○ cannot say/unsure

12) Do you observe any of the following at the very beginning of the seizure? (CHECK ALL THAT APPLY)
- ☐ stopping and staring
- ☐ high-pitched cry
- ☐ humming or other vocalization
- ☐ none of these

13) Does the patient report a change in feeling or sensation during the seizure? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

14) What kind of feeling or sensation? (CHECK ALL THAT APPLY)
- ☐ odd smell
- ☐ odd taste
- ☐ deja vu
- ☐ visual image
- ☐ tunnel vision
- ☐ blurred vision
- ☐ nausea
- ☐ rising feeling in the stomach
- ☐ tingling or numbness
- ☐ pain
- ☐ racing heart
- ☐ dizziness
- ☐ other

15) If "Other", please describe

_____

16) Does the patient shake or stiffen? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

17) How does the shaking or stiffening start? (CHECK ONE ONLY)
- ○ suddenly
- ○ builds up gradually
- ○ cannot say/unsure

18) How does the patient shake or stiffen? (CHECK ONE ONLY)
- ○ on one side only
- ○ on both sides equally
- ○ from one side to the other in the same seizure
- ○ on different sides from one seizure to the next
- ○ cannot say/unsure

19) Does the shaking or stiffening sometimes stop abruptly and then start back up in the same seizure? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

20) How does the shaking or stiffening stop? (CHECK ONE ONLY)
- ○ suddenly
- ○ slows down gradually
- ○ cannot say/unsure

21) How does the patient respond if you talk to them? (CHECK ONE ONLY)
- ○ doesn't respond at all
- ○ looks at you, but doesn't speak or follow commands
- ○ repeats words or speaks nonsense or gibberish
- ○ speaks meaningfully or follows commands
- ○ cannot say/unsure

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22) Can the patient be 'talked out' the seizure? (CHECK ONE ONLY)
- ○ never
- ○ sometimes
- ○ always
- ○ cannot say/Unsure

23) Is the head turned strongly to one side? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

24) Is the head moving side to side? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

25) Are the eyes closed or open? (CHECK ONE ONLY)
- ○ closed
- ○ open
- ○ cannot say/unsure

26) Do you see any of the following during the seizure? (CHECK ALL THAT APPLY)
- ☐ staring
- ☐ wandering around
- ☐ picking at things
- ☐ one arm bent and the other arm stretched out
- ☐ sudden, brief jerks of arms or legs
- ☐ agitated behavior
- ☐ making loud noises
- ☐ sobbing or crying
- ☐ none of these

27) Do you see any of the following during the seizure? (CHECK ALL THAT APPLY)
- ☐ thrashing or 'flopping like a fish'
- ☐ limb movements are 'out of sync'
- ☐ back arching
- ☐ hip thrusting
- ☐ none of these

28) How is the patient breathing during the seizure? (CHECK ONE ONLY)
- ○ normally
- ○ fast and heavy
- ○ not breathing, may turn blue or grey
- ○ cannot say/unsure

29) Does the patient fall during the seizure (or would the patient likely fall if they were not caught? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

30) What does the fall look like? (CHECK ONE ONLY)
- ○ slow, gradual slumping
- ○ sudden collapse or drop
- ○ sudden stiffening and toppling over
- ○ cannot say/unsure

31) How long does the actual seizure activity last? (CHECK ONE ONLY)
- ○ less than 2 minutes
- ○ 2-10 minutes
- ○ > 10 minutes
- ○ cannot say/unsure

32) Right at the end of the seizure activity, do you see any of the following? (CHECK ALL THAT APPLY)
- ☐ cough
- ☐ wipe their nose
- ☐ breathing is noisy and congested
- ☐ none of these

33) Right at the end of the seizure activity, what is their usual level of consciousness and awareness? (CHECK ONE ONLY)
- ○ deeply asleep and won't wake up
- ○ awake but confused and disoriented
- ○ normal
- ○ cannot say/unsure

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Seizure Behavior Second Type

Now, let's talk about the second type of seizure, the one we are calling the _____ seizure

34) Does this seizure type look the same each time, or different? (CHECK ONE ONLY)
- ○ same
- ○ different
- ○ cannot say/Unsure

35) Do you observe any of the following at the very beginning of the seizure? (CHECK ALL THAT APPLY)
- ☐ stopping and staring
- ☐ high-pitched cry
- ☐ humming or other vocalization
- ☐ none of these

36) Does the patient report a change in feeling or sensation during the seizure? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

37) What kind of feeling or sensation? (CHECK ALL THAT APPLY)
- ☐ odd smell
- ☐ odd taste
- ☐ deja vu
- ☐ visual image
- ☐ tunnel vision
- ☐ blurred vision
- ☐ nausea
- ☐ rising feeling in the stomach
- ☐ tingling or numbness
- ☐ pain
- ☐ racing heart
- ☐ dizziness
- ☐ other

38) If "Other", please describe _____

39) Does the patient shake or stiffen? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

40) How does the shaking or stiffening start? (CHECK ONE ONLY)
- ○ suddenly
- ○ builds up gradually
- ○ cannot say/unsure

41) How does the patient shake or stiffen? (CHECK ONE ONLY)
- ○ on one side only
- ○ on both sides equally
- ○ from one side to the other in the same seizure
- ○ on different sides from one seizure to the next
- ○ cannot say/unsure

42) Does the shaking or stiffening sometimes stop abruptly and then start back up in the same seizure? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

43) How does the shaking or stiffening stop? (CHECK ONE ONLY)
- ○ suddenly
- ○ slows down gradually
- ○ cannot say/unsure

44) How does the patient respond if you talk to them? (CHECK ONE ONLY)
- ○ doesn't respond at all
- ○ looks at you, but doesn't speak or follow commands
- ○ repeats words or speaks nonsense or gibberish
- ○ speaks meaningfully or follows commands
- ○ cannot say/unsure

Confidential

45) Can the patient be 'talked out' the seizure? (CHECK ONE ONLY)
- ○ never
- ○ sometimes
- ○ always
- ○ cannot say/Unsure

46) Is the head turned strongly to one side? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

47) Is the head moving side to side? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

48) Are the eyes closed or open? (CHECK ONE ONLY)
- ☐ closed
- ☐ open
- ☐ cannot say/unsure

49) Do you see any of the following during the seizure? (CHECK ALL THAT APPLY)
- ☐ staring
- ☐ wandering around
- ☐ picking at things
- ☐ one arm bent and the other arm stretched out
- ☐ sudden, brief jerks of arms or legs
- ☐ agitated behavior
- ☐ making loud noises
- ☐ sobbing or crying
- ☐ none of these

50) Do you see any of the following during the seizure? (CHECK ALL THAT APPLY)
- ☐ thrashing or 'flopping like a fish'
- ☐ limb movements are 'out of sync'
- ☐ back arching
- ☐ hip thrusting
- ☐ none of these

51) How is the patient breathing during the seizure? (CHECK ONE ONLY)
- ○ normally
- ○ fast and heavy
- ○ not breathing, may turn blue or grey
- ○ cannot say/unsure

52) Does the patient fall during the seizure (or would the patient likely fall if they were not caught? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

53) What does the fall look like? (CHECK ONE ONLY)
- ○ slow, gradual slumping
- ○ sudden collapse or drop
- ○ sudden stiffening and toppling over
- ○ cannot say/unsure

54) How long does the actual seizure activity last? (CHECK ONE ONLY)
- ○ less than 2 minutes
- ○ 2-10 minutes
- ○ > 10 minutes
- ○ cannot say/unsure

55) Right at the end of the seizure activity, do you see any of the following? (CHECK ALL THAT APPLY)
- ☐ cough
- ☐ wipe their nose
- ☐ breathing is noisy and congested
- ☐ none of these

56) Right at the end of the seizure activity, what is their usual level of consciousness and awareness? (CHECK ONE ONLY)
- ○ deeply asleep and won't wake up
- ○ awake but confused and disoriented
- ○ normal
- ○ cannot say/unsure

Seizure Behavior Third Type

Finally, let's talk about the third type of seizure, the one we are calling the _____ seizure.

57) Does this seizure type look the same each time, or different? (CHECK ONE ONLY)
- ○ same
- ○ different
- ○ cannot say/Unsure

58) Do you observe any of the following at the very beginning of the seizure? (CHECK ALL THAT APPLY)
- ☐ stopping and staring
- ☐ high-pitched cry
- ☐ humming or other vocalization
- ☐ none of these

59) Does the patient report a change in feeling or sensation during the seizure? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

60) What kind of feeling or sensation? (CHECK ALL THAT APPLY)
- ☐ odd smell
- ☐ odd taste
- ☐ deja vu
- ☐ visual image
- ☐ tunnel vision
- ☐ blurred vision
- ☐ nausea
- ☐ rising feeling in the stomach
- ☐ tingling or numbness
- ☐ pain
- ☐ racing heart
- ☐ dizziness
- ☐ other

61) If "Other", please describe _____

62) Does the patient shake or stiffen? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

63) How does the shaking or stiffening start? (CHECK ONE ONLY)
- ○ suddenly
- ○ builds up gradually
- ○ cannot say/unsure

64) How does the patient shake or stiffen? (CHECK ONE ONLY)
- ○ on one side only
- ○ on both sides equally
- ○ from one side to the other in the same seizure
- ○ on different sides from one seizure to the next
- ○ cannot say/unsure

65) Does the shaking or stiffening sometimes stop abruptly and then start back up in the same seizure? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

66) How does the shaking or stiffening stop? (CHECK ONE ONLY)
- ○ suddenly
- ○ slows down gradually
- ○ cannot say/unsure

67) How does the patient respond if you talk to them? (CHECK ONE ONLY)
- ○ doesn't respond at all
- ○ looks at you, but doesn't speak or follow commands
- ○ repeats words or speaks nonsense or gibberish
- ○ speaks meaningfully or follows commands
- ○ cannot say/unsure

Confidential

68) Can the patient be 'talked out' the seizure? (CHECK ONE ONLY)
- ○ never
- ○ sometimes
- ○ always
- ○ cannot say/Unsure

69) Is the head turned strongly to one side? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

70) Is the head moving side to side? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

71) Are the eyes closed or open? (CHECK ONE ONLY)
- ☐ closed
- ☐ open
- ☐ cannot say/unsure

72) Do you see any of the following during the seizure? (CHECK ALL THAT APPLY)
- ☐ staring
- ☐ wandering around
- ☐ picking at things
- ☐ one arm bent and the other arm stretched out
- ☐ sudden, brief jerks of arms or legs
- ☐ agitated behavior
- ☐ making loud noises
- ☐ sobbing or crying
- ☐ none of these

73) Do you see any of the following during the seizure? (CHECK ALL THAT APPLY)
- ☐ thrashing or 'flopping like a fish'
- ☐ limb movements are 'out of sync'
- ☐ back arching
- ☐ hip thrusting
- ☐ none of these

74) How is the patient breathing during the seizure? (CHECK ONE ONLY)
- ○ normally
- ○ fast and heavy
- ○ not breathing, may turn blue or grey
- ○ cannot say/unsure

75) Does the patient fall during the seizure (or would the patient likely fall if they were not caught? (CHECK ONE ONLY)
- ○ no
- ○ yes
- ○ cannot say/unsure

76) What does the fall look like? (CHECK ONE ONLY)
- ○ slow, gradual slumping
- ○ sudden collapse or drop
- ○ sudden stiffening and toppling over
- ○ cannot say/unsure

77) How long does the actual seizure activity last? (CHECK ONE ONLY)
- ○ less than 2 minutes
- ○ 2-10 minutes
- ○ > 10 minutes
- ○ cannot say/unsure

78) Right at the end of the seizure activity, do you see any of the following? (CHECK ALL THAT APPLY)
- ☐ cough
- ☐ wipe their nose
- ☐ breathing is noisy and congested
- ☐ none of these

79) Right at the end of the seizure activity, what is their usual level of consciousness and awareness? (CHECK ONE ONLY)
- ○ deeply asleep and won't wake up
- ○ awake but confused and disoriented
- ○ normal
- ○ cannot say/unsure

Feedback

Please tell us how you felt about completing this survey. Your responses will be anonymous.

	Strongly Disagree	Somewhat Disagree	Neither Agree nor Disagree	Somewhat Agree	Strongly Agree
80) I felt comfortable.	☐	☐	☐	☐	☐
81) I felt interested.	☐	☐	☐	☐	☐
82) I felt curious.	☐	☐	☐	☐	☐
83) I felt embarrassed.	☐	☐	☐	☐	☐
84) I felt upset.	☐	☐	☐	☐	☐

85) If you felt uncomfortable, embarassed or upset, please tell us why you felt this way: _____

How willing would you be to answer these questions in the office of a doctor you just met

	Very Willing	Somewhat Willing	Mixed Feelings	Somewhat Unwilling	Very Unwilling
86) in a face-to-face interview?	☐	☐	☐	☐	☐
87) on a paper questionnaire?	☐	☐	☐	☐	☐
88) on a computer?	☐	☐	☐	☐	☐

89) If you would be unwilling, please tell us why might feel this way: _____

9.3 IDIC-15 Study Case Report Form

VALIDATION STUDY OF THE DIAGNOSIS OF IDIC(15) SYNDROME

Case Report Form

Version 2.0, 21/04/2015

Rater's initials /__/__/ Patient's initials /__/__/

Rater's background:

_____

Date of birth /__/__//__/__//__/__/ Sex /M/ /F/

Weight Kg %ile

Height cm %ile

CC cm %ile

<u>Step 1. Medical records</u>

Past & present history

Gestation week at delivery /__/__/ Apgar score /__/__/

Birth weight Kg %ile Length at birth cm %ile CC cm %ile

Feeding difficulties in newborn period /No/ /Yes/

Standing /No/ /Yes/ Age, months /__/__/ Age unknown /__/

Walking /No/ /Yes/ Age, months /__/__/ Age unknown /__/

Speech /No/ /Yes/ Age, months /__/__/ Age unknown /__/

Only minimal number of words /__/

Self-feeding /No/ /Yes/ Age, months /__/__/ Age unknown /__/

Playing /No/ /Yes/ Age, months /__/__/ Age unknown /__/

Recurrent upper respiratory tract infections during infancy	/No/	/Yes/	/Unknown/	
Constipation	/No/	/Yes/		
Hypogonadism	/No/	/Yes/	/Unknown/	
Urinary tract defects	/No/	/Yes/	/Unknown/	
Congenital heart defects	/No/	/Yes/	/Unknown/	
Unilateral renal agenesis	/No/	/Yes/	/Unknown/	
Umbilical hernias	/No/	/Yes/	/Unknown/	
Inguinal hernias	/No/	/Yes/	/Unknown/	
General examination				
Growth restriction	/No/	/Yes/	/Unknown/	
Microcephaly	/No/	/Yes/	/Unknown/	
Macrocephaly	/No/	/Yes/	/Unknown/	
Flat occiput	/No/	/Yes/	/Unknown/	
Occipital groove	/No/	/Yes/	/Unknown/	
High forehead	/No/	/Yes/	/Unknown/	
Frontal bossing	/No/	/Yes/	/Unknown/	
Epicanthal folds	/No/	/Yes/	/Unknown/	
Deep set eyes	/No/	/Yes/	/Unknown/	
Downslanting palpebral fissures	/No/	/Yes/	/Unknown/	
Synophrys	/No/	/Yes/	/Unknown/	
Low-set and posteriorly rotated ears	/No/	/Yes/	/Unknown/	
Broad nose	/No/	/Yes/	/Unknown/	
Short philtrum	/No/	/Yes/	/Unknown/	
Anteverted nares	/No/	/Yes/	/Unknown/	
Midface hypoplasia	/No/	/Yes/	/Unknown/	
Large incisors	/No/	/Yes/	/Unknown/	

Cleft palate/highly arched palate	/No/	/Yes/	/Unknown/
Protruding tongue	/No/	/Yes/	/Unknown/
Drooling	/No/	/Yes/	/Unknown/
Prognathia	/No/	/Yes/	/Unknown/
Wide mouth	/No/	/Yes/	/Unknown/
Wide spaced teeth	/No/	/Yes/	/Unknown/
Hypopigmented skin (compared to family)	/No/	/Yes/	/Unknown/
Light hair color (compared to family)	/No/	/Yes/	/Unknown/
Light eye color (compared to family)	/No/	/Yes/	/Unknown/
Hyperactive lower extremities	/No/	/Yes/	/Unknown/
Uplifted, flexed arms during ambulation	/No/	/Yes/	/Unknown/ Present at visit /__/
Joint hyperlaxity	/No/	/Yes/	/Unknown/ Present at visit /__/
Clinodactyly	/No/	/Yes/	/Unknown/
Syndactyly	/No/	/Yes/	/Unknown/
Brachydactyly	/No/	/Yes/	/Unknown/
Scoliosis	/No/	/Yes/	/Unknown/
Obesity	/No/	/Yes/	/Unknown/

Neurological examination

Normal	/No/	/Yes/	/Unknown/	If no, please indicate abnormal findings:
Hypotonia	/No/	/Yes/	/Unknown/	Present at visit /__/
Wide-based gait with pronated or valgus-positioned ankles	/No/	/Yes/	/Unknown/	
Ataxia	/No/	/Yes/	/Unknown/	Present at visit /__/
Clumsiness	/No/	/Yes/	/Unknown/	Present at visit /__/
Jerky motions	/No/	/Yes/	/Unknown/	Present at visit /__/
Tremor	/No/	/Yes/	/Unknown/	Present at visit /__/
Swallowing disorders	/No/	/Yes/	/Unknown/	Present at visit /__/

Strabismus /No/ /Yes/ /Unknown/

Brisk deep tendon reflexes /No/ /Yes/ /Unknown/ Present at visit /__/

Increased sensitivity to heat /No/ /Yes/ /Unknown/

Abnormal sleep-wake cycles /No/ /Yes/ /Unknown/

Overall judgment of developmental delay /No/ /Mild/ /Moderate/ /Severe/ /Unknown/

Mental retardation / No/ /Mild/ /Moderate/ /Severe/ /Unknown/

Psychiatric examination

Normal /No/ /Yes/ /Unknown/ If no, please indicate abnormal findings:

Laughter/smiling /No/ /Yes/ /Unknown/ Present at visit /__/

Happy demeanor /No/ /Yes/ /Unknown/ Present at visit /__/

Easily excitable /No/ /Yes/ /Unknown/ Present at visit /__/

Echolalia /No/ /Yes/ /Unknown/ Present at visit /__/

Hand-flapping movements /No/ /Yes/ /Unknown/ Present at visit /__/

Hypermotoric behavior /No/ /Yes/ /Unknown/ Present at visit /__/

Tantrums /No/ /Yes/ /Unknown/ Present at visit /__/

Stubbornness /No/ /Yes/ /Unknown/ Present at visit /__/

Verbal perseverance /No/ /Yes/ /Unknown/ Present at visit /__/

Skin picking /No/ /Yes/ /Unknown/ Present at visit /__/

Hyperphagia /No/ /Yes/ /Unknown/

Anxiety /No/ /Yes/ /Unknown/ Present at visit /__/

Emotional lability /No/ /Yes/ /Unknown/ Present at visit /__/

Impulsivity /No/ /Yes/ /Unknown/ Present at visit /__/

Aggressiveness /No/ /Yes/ /Unknown/ Present at visit /__/

Epilepsy /No/ /Yes/ /Unknown/ If yes, please complete the following:

Infantile spasms	/No/	/Yes/	/Unknown/
Generalized tonic-clonic seizures	/No/	/Yes/	/Unknown/
Myoclonic seizures	/No/	/Yes/	/Unknown/
Atypical absence seizures	/No/	/Yes/	/Unknown/
Axial tonic seizures	/No/	/Yes/	/Unknown/
Focal seizures	/No/	/Yes/	/Unknown/
Refractory epilepsy	/No/	/Yes/	/Unknown/

Autistic behavior /No/ /Yes/ /Unknown/ If yes, please complete the following:

ADOS score:_____

Diagnosis 1.

15q11-13 Duplication Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
Angelman Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
Pitt-Hopkins Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
Mowat-Wilson Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
Mucopolysaccharidosis type 3	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
FOXG1 Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
West Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
Autism spectrum disorder	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
Other neurodevelopmental disorder	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**

Please, specify:

…….

<u>Step 2. Video-recording</u>			
General examination			
Growth restriction	/No/	/Yes/	/Unknown/
Microcephaly	/No/	/Yes/	/Unknown/
Macrocephaly	/No/	/Yes/	/Unknown/
Flat occiput	/No/	/Yes/	/Unknown/
Occipital groove	/No/	/Yes/	/Unknown/
High forehead	/No/	/Yes/	/Unknown/
Frontal bossing	/No/	/Yes/	/Unknown/
Epicanthal folds	/No/	/Yes/	/Unknown/
Deep set eyes	/No/	/Yes/	/Unknown/
Downslanting palpebral fissures	/No/	/Yes/	/Unknown/
Synophrys	/No/	/Yes/	/Unknown/
Low-set and posteriorly rotated ears	/No/	/Yes/	/Unknown/
Broad nose	/No/	/Yes/	/Unknown/
Short philtrum	/No/	/Yes/	/Unknown/
Anteverted nares	/No/	/Yes/	/Unknown/
Midface hypoplasia	/No/	/Yes/	/Unknown/
Large incisors	/No/	/Yes/	/Unknown/
Cleft palate/highly arched palate	/No/	/Yes/	/Unknown/
Protruding tongue	/No/	/Yes/	/Unknown/
Drooling	/No/	/Yes/	/Unknown/
Prognathia	/No/	/Yes/	/Unknown/
Wide mouth	/No/	/Yes/	/Unknown/
Wide spaced teeth	/No/	/Yes/	/Unknown/
Hypopigmented skin (compared to family)	/No/	/Yes/	/Unknown/
Light hair color (compared to family)	/No/	/Yes/	/Unknown/
Light eye color (compared to family)	/No/	/Yes/	/Unknown/

Hyperactive lower extremities /No/ /Yes/ /Unknown/

Uplifted, flexed arms during ambulation /No/ /Yes/ /Unknown/ Present at visit /__/

Joint hyperlaxity /No/ /Yes/ /Unknown/ Present at visit /__/

Clinodactyly /No/ /Yes/ /Unknown/

Syndactyly /No/ /Yes/ /Unknown/

Brachydactyly /No/ /Yes/ /Unknown/

Scoliosis /No/ /Yes/ /Unknown/

Obesity /No/ /Yes/ /Unknown/

Neurological examination

Normal /No/ /Yes/ /Unknown/ If no, please indicate abnormal findings:

Hypotonia /No/ /Yes/ /Unknown/ Present at visit /__/

Wide-based gait with pronated or valgus-positioned ankles /No/ /Yes/ /Unknown/

Ataxia /No/ /Yes/ /Unknown/ Present at visit /__/

Clumsiness /No/ /Yes/ /Unknown/ Present at visit /__/

Jerky motions /No/ /Yes/ /Unknown/ Present at visit /__/

Tremor /No/ /Yes/ /Unknown/ Present at visit /__/

Swallowing disorders /No/ /Yes/ /Unknown/ Present at visit /__/

Strabismus /No/ /Yes/ /Unknown/

Brisk deep tendon reflexes /No/ /Yes/ /Unknown/ Present at visit /__/

Increased sensitivity to heat /No/ /Yes/ /Unknown/

Abnormal sleep-wake cycles /No/ /Yes/ /Unknown/

Overall judgment of developmental delay /No/ /Mild/ /Moderate/ /Severe/ /Unknown/

Mental retardation / No/ /Mild/ /Moderate/ /Severe/ /Unknown/

Psychiatric examination

Normal /No/ /Yes/ /Unknown/ If no, please indicate abnormal findings:

Laughter/smiling	/No/	/Yes/	/Unknown/	Present at visit /__/
Happy demeanor	/No/	/Yes/	/Unknown/	Present at visit /__/
Easily excitable	/No/	/Yes/	/Unknown/	Present at visit /__/
Echolalia	/No/	/Yes/	/Unknown/	Present at visit /__/
Hand-flapping movements	/No/	/Yes/	/Unknown/	Present at visit /__/
Hypermotoric behavior	/No/	/Yes/	/Unknown/	Present at visit /__/
Tantrums	/No/	/Yes/	/Unknown/	Present at visit /__/
Stubbornness	/No/	/Yes/	/Unknown/	Present at visit /__/
Verbal perseverance	/No/	/Yes/	/Unknown/	Present at visit /__/
Skin picking	/No/	/Yes/	/Unknown/	Present at visit /__/
Hyperphagia	/No/	/Yes/	/Unknown/	
Anxiety	/No/	/Yes/	/Unknown/	Present at visit /__/
Emotional lability	/No/	/Yes/	/Unknown/	Present at visit /__/
Impulsivity	/No/	/Yes/	/Unknown/	Present at visit /__/
Aggressiveness	/No/	/Yes/	/Unknown/	Present at visit /__/

Autistic behavior / No/ /Yes/ /Unknown/ If yes, please complete the following:

Diagnosis 2.

15q11-13 Duplication Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
Angelman Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
Pitt-Hopkins Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
Mowat-Wilson Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
Mucopolysaccharidosis type 3	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
FOXG1 Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
West Syndrome	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**

Autism spectrum disorder	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**
Other neurodevelopmental disorder	**/No/**	**/Yes/**	**/Probable/**	**/Uncertain/**

Please, specify:

…….

Step 3. Instrumental tests

EEG /Normal/ /Aspecific/ /Abnormal/ /Unknown/

If abnormal, please complete the following:

Abnormal background rhythm /No/ /Yes/ /Unknown/

Spikes /No/ /Yes/ /Unknown/

Slow waves /No/ /Yes/ /Unknown/

Spike-slow waves /No/ /Yes/ /Unknown/

Polyspike-slow waves /No/ /Yes/ /Unknown/

Very high amplitude fast activity /No/ /Yes/ /Unknown/

Other epileptiform /No/ /Yes/ /Unknown/

Other, specify: ……

MRI /Normal/ /Aspecific/ /Abnormal/ /Unknown/

Please, specify: ……

CT-Scan /Normal/ /Aspecific/ /Abnormal/ /Unknown/

Please, specify: ……

Diagnosis 3.

15q11-13 Duplication Syndrome /No/ /Yes/ /Probable/ /Uncertain/

Angelman Syndrome /No/ /Yes/ /Probable/ /Uncertain/

Pitt-Hopkins Syndrome /No/ /Yes/ /Probable/ /Uncertain/

Mowat-Wilson Syndrome /No/ /Yes/ /Probable/ /Uncertain/

Mucopolysaccharidosis type 3 /No/ /Yes/ /Probable/ /Uncertain/

FOXG1 Syndrome /No/ /Yes/ /Probable/ /Uncertain/

West Syndrome /No/ /Yes/ /Probable/ /Uncertain/

Autism spectrum disorder /No/ /Yes/ /Probable/ /Uncertain/

Other neurodevelopmental disorder /No/ /Yes/ /Probable/ /Uncertain/

Please, specify:

…….

9.4 EPIRES Study Case Report Form

EPIRES STUDY Case report Form

(Version 1.0, 01/07/2011)

Center code: Patient's code:

Sex: M [_] F [_]

Birth date: _____

Residency: _____

Telephone: _____

General Practitioner: _____

Living status : Alone [_]

Hausemates [_]

Partner/family [_]

Marital status: Married [_] Single [_]

Divorced [_] Widowed [_]

Occupazione:

Employed [_] Student [_] Retired [_]

Employment: _____ Unemployed [_]

The patient is currently followed by this center: YES [_] NO [_]

Last visit date: __/__/____

EEG: _____ Caring neurologist:_____

If the patient is not longer followed by this center, please specify the reason:

Deceased [_] Cause of death: _____
Compliance [_]
Unknown [_]

Family history for epilepsy: YES [_] NO [_]

EPILEPSY DIAGNOSI: YES [_]

NO [_]

(If not, please specify) Acute symptomatic seizure [_]

Pseudo-seizures [_]

Other paroxsysmal events [_]

Other [_]

- Date of the diagnosis: __/__/____

Type of seizures

Partial	**[_]**
Generalized	**[_]**
Undetermined	**[_]**

- Date of the first seizure: __/__/____

EPILEPTIC SYNDROME

Partial symptomatic	**[_]**
Partial idiopathic	**[_]**
Partial cryptogenic	**[_]**
Generalized idiopathic	**[_]**
Generalizzata cryptogenic	**[_]**
Generalizzata symptomatic	**[_]**
Syntomatic • **Aspecific etiology** • **Specific syndrome**	 **[_]** **[_]**
Undetermined syndrome • **With partial and generaized seizures** • **without partial and generaized seizures**	 **[_]** **[_]**
Other syndromes	**[_]**

Is epilepsy associated with structural, metabolic or other disorders?

- Infections [_]
- Cerebrovascular diseases [_]
- Brain injury [_]
- Brain tumor [_]
- Metabolic and toxic encephalopathies [_]
- Degenerative brain disordes [_]
- Mesial temporal sclerosis [_]
- Neurocutaneous disorders [_]
- Brain developement disorders [_]
- Progressive myoclonic epilepsy [_]
- Genetic disorders [_]
- Other [_]

Had the patient period of remission? YES [_] NO [_]

Number of periods of remission: _____

	START DATE	**END DATE**	**ONGOING**
First remission			[_]
Second remission			[_]
Third remission			[_]
Fourth remission			[_]
Fifth remission			[_]
Sixth remission			[_]
Seventh remission			[_]
Eighth remission			[_]
Ninth remission			[_]
Tenth remission			[_]

ANTIEPILEPTIC DRUG THERAPY

Drug	MAXIMUM TOTAL DAILY DOSE	ADMINISTRATION ROUTE	START DATE	END DATE	DRUG WITHDRAWAL	REASON FOR WITHDRAWAL
1.					YES [_] NO [_]	
2.					YES [_] NO [_]	
3.					YES [_] NO [_]	
4.					YES [_] NO [_]	
5.					YES [_] NO [_]	
6.					YES [_] NO [_]	
7.					YES [_] NO [_]	
8.					YES [_] NO [_]	
9.					YES [_] NO [_]	
10.					YES [_] NO [_]	
11.					YES [_] NO [_]	
12.					YES [_] NO [_]	
13.					YES [_] NO [_]	
14.					YES [_] NO [_]	
15.					YES [_] NO [_]	